



Ramachandran

PHARMACOLOGY
RECALL

PHARMACOLOGY RECALL

SECOND
EDITION

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SECOND
EDITION



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Section I

Principles of Pharmacology

Principles of Pharmacology

Section I

1

Introduction to Pharmacology

What is pharmacology?

The study of the interaction between chemicals and living systems

What is a drug?

A drug is broadly defined as any chemical agent that affects biologic systems.

Name and define the four major subdivisions of pharmacology.

1. **Pharmacokinetics**—describes “what the body does to the drug.” This includes topics such as absorption, distribution, metabolism, and excretion of drugs.
2. **Pharmacodynamics**—describes “what the drug does to the body.” Specifically, it deals with the biochemical and physiological effects of drugs and their mechanisms of action.
3. **Pharmacotherapeutics**—describes the use of drugs for the prevention, diagnosis, and treatment of disease.
4. **Toxicology**—describes the undesirable effects of therapeutic agents, poisons, and pollutants on biologic systems.

For each of the following endings, name the classification of drug and give an example:

-azine

phenothiazine-like antipsychotics (e.g., chlorpromazine)

-ane

volatile general anesthetics (e.g., halothane)

-azepam

antianxiety drugs (e.g., diazepam)

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-bital	barbiturate sedative hypnotic drugs (e.g., phenobarbital)
-caine	local anesthetics (e.g., cocaine)
-cillin	penicillins (e.g., nafcillin)
-cycline	tetracycline-type antibiotics (e.g., doxycycline)
-olol	β -blockers (e.g., propranolol)
-opril	ACE inhibitors (e.g., captopril)
-statin	HMG-CoA reductase inhibitors (e.g., lovastatin)
-zosin	postsynaptic α -receptor blockers (e.g., terazosin)

Should trade names be memorized for the Boards?

✎ In the past the Boards have not tested trade names. It is best to first learn the generic name. Trade names have been provided only for future reference.

Do I need to know every characteristic of every drug?

No. However, it is absolutely critical that you at least remember the classification, mechanism of action, therapeutic use, and life threatening or unique adverse effects of all of the major drugs.

2

Pharmacokinetics

Define pharmacokinetics.

Pharmacokinetics describes **actions of the body on drugs**, including the principles of drug **absorption, distribution, biotransformation (metabolism), and excretion.**

ABSORPTION

Define absorption.

Absorption is the rate at which and extent to which a drug moves from its site of administration.

What does the rate and efficacy of absorption depend on?

Route of administration—The intravenous route is most effective.

Blood flow—Highly vascularized organs such as the small intestine have the greatest absorbing ability.

Surface area available—Absorption of a drug is directly proportional to the surface area available.

Solubility of a drug—The ratio of hydrophilic to lipophilic properties (**partition coefficient**) that a drug has will determine whether the drug can permeate cell membranes.

Drug-drug interactions—When given in combination, drugs can either enhance or inhibit one another's absorption.

pH—A drug's acidity or alkalinity affects its charge, which affects absorption.

In what way does the pH of a drug affect its charge?

Many drugs are either weak acids or weak bases. Acidic drugs are **uncharged** when protonated:



Basic drugs are **charged** when protonated:



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How does charge affect a drug's ability to permeate a cell membrane?

Generally, a drug will pass through cell membranes more easily if it is uncharged. Therefore, the amount of drug absorbed depends upon its ratio of charged to uncharged species, which is determined by the ambient pH at the site of administration and the pK_a (negative log of dissociation constant) of the drug (Figure 2-1).

Define bioavailability.

The fraction of administered drug that gains access to its site of action or a biologic fluid that allows access to the site of action

What is the bioavailability of an intravenously injected drug?

100%—because all of the drug enters the systemic circulation

What is the bioavailability of any drug that is not intravascularly injected?

Less than 100%—because some of the drug may not be absorbed, or it may become inactivated

What factors affect bioavailability?

1. First-pass metabolism
2. All of the factors that affect absorption

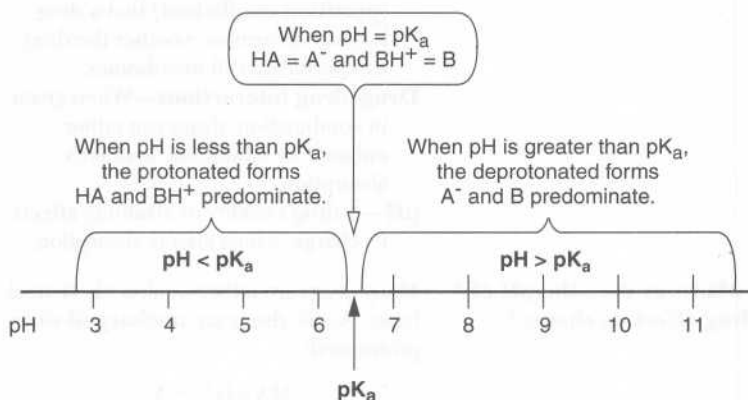


Figure 2-1. The distribution of a drug between its ionized and un-ionized form depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 6.)

What factors affect bio-availability?

1. First-pass metabolism
2. All of the factors that affect absorption (i.e., pH, blood flow, drug solubility, drug-drug interactions, route of administration)

What is first-pass metabolism?

Biotransformation that occurs before the drug reaches its site of action. It most commonly occurs in the liver. (For example, orally administered nitroglycerin is said to have a high first-pass metabolism because 90% of it is inactivated by the liver. Morphine is another important drug that has a high first-pass metabolism.)

What are the routes of drug administration?

Alimentary
Parenteral
Inhalation
Topical
Transdermal
Subcutaneous

Name the four types of alimentary routes of administration and state the advantage of each.

1. Oral—commonest route. *Advantages* include convenience/patient compliance and the utilization of the small intestine, which is specialized for absorption because of its large surface area.
2. Buccal (between gum and cheeks). *Advantage:* Allows direct absorption into the venous circulation
3. Sublingual (under the tongue)—Nitroglycerin is often given by this route. *Advantage:* Allows the drug to drain into the superior vena cava, thus bypassing hepatic first-pass metabolism.
4. Rectal (suppository)—Useful when the oral route is unavailable due to vomiting or loss of consciousness. *Advantage:* Approximately 50% of drug absorbed from the rectum will bypass the liver.

Name the four parenteral routes of administration and state the advantage of each.

1. Intravenous—direct injection into the vascular system. *Advantage:* Most rapid and potent mode of administration, because 100% of drug enters the circulation.

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2. **Intramuscular—*Advantages:*** Usually more rapid and complete absorption than with oral administration. Minimizes hazards of intravascular injection.
3. **Subcutaneous—*Advantages:*** Same as intramuscular.
4. **Intrathecal—*Advantage:*** In cases of acute CNS infections or spinal anesthesia, drugs can be more effective if injected directly into the spinal subarachnoid space.

What category of drugs is commonly administered by inhalation?

Pulmonary agents

How are inhaled drugs administered?

By machine aerosolization or vaporization

When is topical administration used?

Usually for treatment of localized disease (e.g., psoriasis, acne, eye infections)

When is transdermal administration used?

For sustained release of a drug—for example, nicotine patches

DISTRIBUTION

Define distribution.

The process by which a drug leaves the bloodstream and enters the interstitium or the cells of the tissues

By what three biochemical mechanisms are drugs absorbed into cells?

1. **Passive diffusion**—governed by a concentration gradient across a membrane, which makes a drug move from an area of high concentration to one of low concentration. It is the **most common** mode of drug transport
2. **Transport by special carrier proteins**—a form of passive diffusion that is facilitated by a carrier protein
3. **Active transport**—transport against a concentration gradient. The energy for this mechanism comes from dephosphorylation of adenosine triphosphate.

What does distribution depend upon?

Blood flow

Capillary permeability—The structure

of capillaries varies depending on the organ. For example, in the brain the junction between cells is very tight. In the liver and spleen, the junction between endothelial cells is wide, which allows large molecules to pass through.

Binding to plasma proteins such as albumin—This will limit access to cellular compartments.

Drug structure—Small lipophilic molecules will be able to distribute to more compartments than will large polar molecules.

BIOTRANSFORMATION

Why does the body biotransform drugs?

The lipophilic properties of drugs that allow them to pass through cell membranes hinder their elimination. Therefore, drugs are modified to become more polar so that elimination can occur more quickly.

What are the two general sets of modifications that occur in biotransformation?

They are known as phase I and phase II reactions.

What happens in a phase I reaction?

Lipophilic molecules are converted into more-polar molecules by introduction of, or unmasking of, a polar functional group.

What types of phase I reactions occur?

Oxidation, reduction (dehydrogenation), and hydrolysis

What happens in phase II conjugation reactions?

Formation of a covalent linkage between functional groups on the parent drug and another substrate

Specifically, what substrates are added in phase II conjugation reactions?

Glucuronate—Quantitatively, addition of this substrate constitutes the most important conjugation reaction.

Acetic acid
Glutathione
Sulfate

In what organ do phase I and phase II reactions occur?

Primarily in the liver

- Where do these reaction occur on a cellular level?** Phase I reactions occur in the endoplasmic reticulum.
Phase II reactions occur in the cytosol.
- What factors affect drug biotransformation?** Genetic differences—Each individual has a varying capacity to metabolize a drug through a given pathway. (For example, some individuals are slow acetylators and therefore cannot rapidly inactivate drugs such as isoniazid, procainamide, and hydralazine.)
Induction of the cytochrome P-450 system—may increase biotransformation
Inhibition of the cytochrome P-450 system—If two drugs or compounds are competing for the active site of the same enzyme, then one of the drugs will have a decreased rate of transformation.
Disease, especially of the liver
Age and gender
- Are the rates for drug biotransformation predictable?** Yes. In general, drugs will be inactivated or biotransformed according to one of two general chemistry principles: first-order and zero-order kinetics.
- Define first-order kinetics.** Process by which a constant percentage of substrate is metabolized per unit time. (For example: Ten percent of a certain drug [concentration, 100 mg/dL] is eliminated every 2 hours; 2 hours later, the concentration will be 90 mg/dL; in 4 hours it will be 81 mg/dL; and so on.) The higher the concentration of drug, the greater the absolute amount of drug biotransformed or excreted per unit of time.
- Describe zero-order kinetics.** Process by which a constant amount of drug is metabolized per unit of time regardless of the drug concentration. (For example: If a drug concentration is 100 mg/dL and the body can remove 5 mg/dL every hour, then 1 hour later the concentration will be 95 mg/dL; 2 hours

later it will be 90 mg/dL; and so on.) Alcohol is metabolized according to zero-order kinetics.

EXCRETION

What is excretion?

The process by which a drug or metabolite is removed from the body

What is the difference between excretion and secretion?

Excretion is the removal of a drug from the body.

Secretion occurs when the drug is actively transported from one compartment into another. (For example: Drugs are *secreted* into the renal tubule from the medullary capillaries.)

What are the major routes of excretion?

Renal—urine is one of the most common routes of elimination

Fecal

Respiration—primarily for anesthetic gases and vapors

Breast milk

Skin

3

Pharmacodynamics

Define pharmacodynamics.

Pharmacodynamics describes the actions of a drug on the body, and includes the principles of receptor interactions, mechanisms of therapeutic and toxic action, and dose-response relationships.

How is pharmacodynamics related to pharmacokinetics?

The pharmacokinetic processes of absorption, distribution, biotransformation, and excretion determine how quickly and to what extent a drug will appear at a target site. Pharmacodynamics concepts explain the pharmacological effects of drugs and their mechanism of action (Figure 3-1).

RECEPTOR INTERACTIONS

What is a receptor?

A macromolecule typically made of proteins that interacts with either an endogenous ligand or a drug to mediate a pharmacologic or physiologic effect

What are the two main functions of receptors?

1. Ligand binding
2. Activation of an effector system (message propagation)

What is an effector?

Effectors transduce drug-receptor interactions into cellular effects. There are four types of well-known effector mechanisms:

1. **Transmembrane**—Some ligands such as insulin bind to receptors that have both an extracellular and intracellular component. Binding of the extracellular component stimulates the intracellular component, which is coupled to an enzyme, for example, tyrosine kinase.
2. **Ligand-gated ion channels**—Drugs bind to these receptors, which then

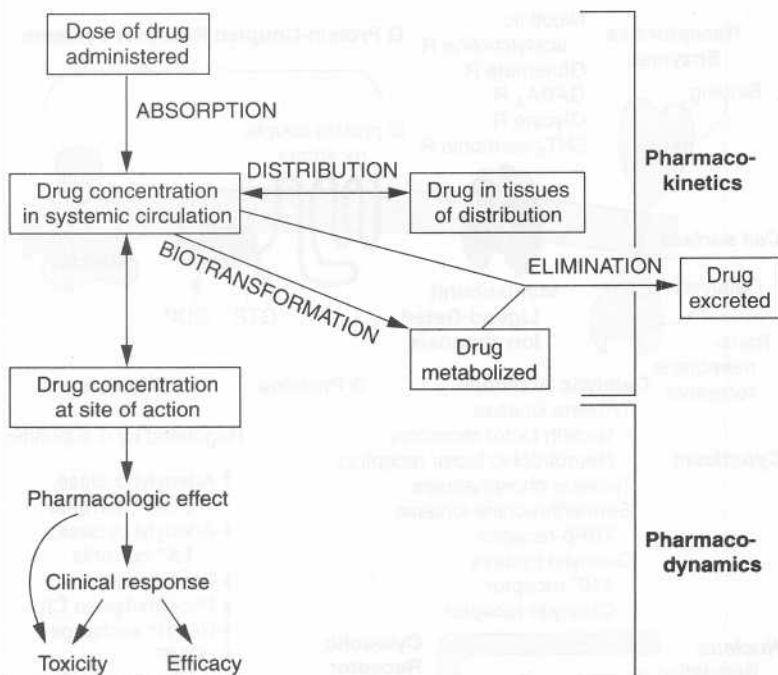


Figure 3-1. The relationship between dose and effect can be separated into pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) components. Concentration provides the link between pharmacokinetics and pharmacodynamics and is the focus of the target concentration approach to rational dosing. The three primary processes of pharmacokinetics are absorption, distribution, and elimination. (Redrawn from Katzung BG: *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT, Appleton & Lange, 1998, p 35.)

alter the conductance of ions through the cell membrane channels.

Examples of ligand-gated ion channel drugs are benzodiazepines and acetylcholine.

3. **Intracellular**—Thyroid and steroid hormones bind to nuclear receptors to form complexes that interact with DNA, which causes changes in gene expression.
4. **Second messenger system**—Drugs bind to receptors that activate second messenger systems involving G proteins (Figure 3-2).

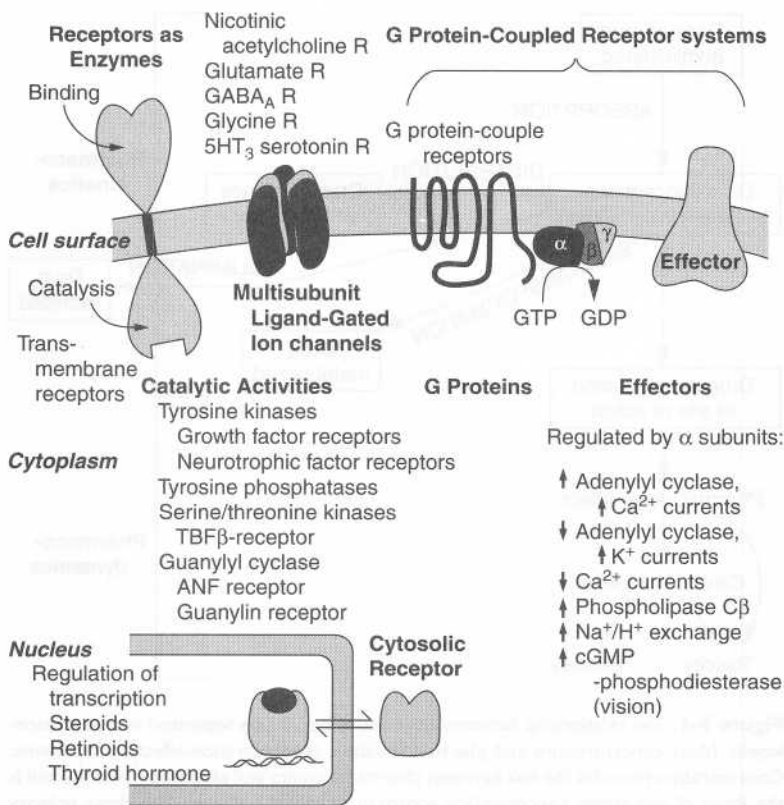


Figure 3-2. Classification of physiological receptors and their relationships to signaling pathways. (Redrawn from Hardman JG, Limbird LE [eds]: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th ed. New York, McGraw-Hill, 1996, p 32. Used with permission of The McGraw-Hill Companies.)

What are second messenger systems?

Second messenger systems allow signals from cell surface receptors to be converted and amplified into a cellular response.

What are the three best-known second messenger systems, and which enzyme produces each of them?

1. Cyclic adenosine monophosphate (cAMP)—produced by adenylate cyclase
2. Cyclic guanosine monophosphate (cGMP)—produced by guanylate cyclase
3. Inositol triphosphate (IP₃)—produced by phospholipase C

MECHANISMS OF THERAPEUTIC AND TOXIC ACTION

What is an agonist?	A drug that binds to and activates receptors
What is a full agonist?	A drug that, when bound to a receptor, produces 100% of the maximum possible biologic response
What are partial agonists?	Drugs that produce less than 100% of the maximum possible biologic response no matter how high their concentration
What are antagonists?	Drugs that bind to receptors or other drugs and <i>inhibit</i> a biologic response
What does a competitive antagonist do?	It binds <i>reversibly</i> to the same active site of an enzyme as an agonist.
How can a competitive antagonist be overcome?	By increasing the concentration of the drug (agonist). The maximum efficacy of the drug will not change in the presence of a competitive antagonist.
What does a noncompetitive antagonist do?	It binds irreversibly to a different site on the enzyme than the antagonist. Noncompetitive agonists <i>cannot</i> be overcome by increasing concentrations of the drug.
How will the maximum efficacy of a drug be affected by such noncompetitive antagonists?	Maximum efficacy will be <i>reduced</i> in the presence of a noncompetitive antagonist (Figure 3-3).

DOSE-RESPONSE RELATIONSHIPS

What is the difference between efficacy and potency?	Efficacy is the ability to produce a biologic effect. Potency is related to the amount of drug necessary to cause a biologic effect.
Give an example of efficacy.	If two drugs, drug A and drug B, are both claimed to reduce a patient's heart rate by 25%, then they both have the same efficacy.
Give an example of potency.	Only 1 mg of drug A needs to be given to

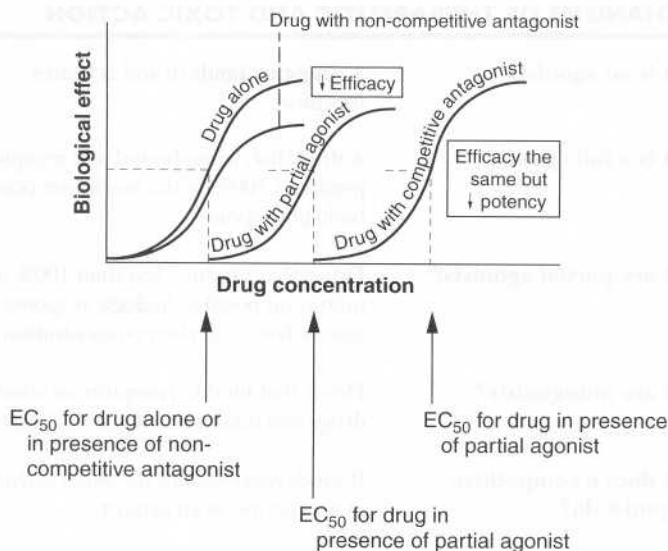


Figure 3-3. Effects of drug antagonists and partial agonist. EC_{50} = drug dose that shows 50% of maximal response. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 22.)

achieve a reduction in heart rate, whereas 10 mg of drug B are needed. Therefore, it can be inferred that drug A is more potent.

What is K_d ?

The concentration of drug yielding 50% occupancy of the receptor (dissociation constant)

What is EC_{50} ?

The drug concentration that produces 50% of the maximum possible response in a graded dose-response curve (see Figure 3-3).

4

Drug Dosing and Prescription Writing

DRUG DOSING

What three factors are involved in determining an appropriate drug dose for a patient?

1. Type of infection or disease
2. Patient variables (e.g., weight, liver or kidney disease)
3. Plasma concentration needed to achieve efficacy

What is volume of distribution (V_d)?

The apparent volume into which a drug is able to distribute

How is V_d calculated?

$V_d = \text{total drug in the body} \div \text{plasma concentration of the drug}$

What is the significance of a large V_d ?

Based on the equation presented above, a large V_d signifies that most of the drug is being sequestered in some organ or compartment.

What is a maintenance dose?

A dose of a drug given to achieve a therapeutic plasma concentration over an extended period of time

What is the equation for calculating a maintenance dose?

Maintenance dose = clearance \times desired plasma concentration

What is important to remember in performing this calculation?

You must be absolutely certain that the units are correct.

What is a loading dose?

In some clinical situations the desired plasma concentration of a drug must be achieved rapidly. In these cases a single **loading dose** is injected, followed by a routine maintenance dose.

What is the equation for calculating a loading dose?	Loading dose = $V_d \times$ desired plasma concentration
Define peak and trough concentrations.	These are maximum and minimum plasma concentrations, respectively, which are observed during dosing intervals.
What variable affects these concentrations?	They will fluctuate around the steady-state plasma concentration (C_{ss}).
What is the steady-state plasma concentration?	The point at which the rate of drug availability is equal to the rate of drug elimination
How does frequency of dosing affect the steady-state concentration?	It will not change.
What factors will dosing frequency affect?	Using smaller doses more frequently will help minimize swings in drug concentration (i.e., maximum and minimum plasma concentrations). See Figure 4-1.
How many half-lives are required to reach steady-state concentration?	Approximately 4½ half-lives. At 3.3×, the half-life of the drug will reach 90% of its effective half-life.
What is clearance?	Clearance is defined as the volume of plasma cleared of drug per unit of time.
What is an excretion rate?	The rate at which a drug is eliminated from the body, which is measured by clearance \times plasma concentration
What is a therapeutic index?	The ratio of a drug's toxic dose to its therapeutic dose. A safe drug will have a high therapeutic index. See Appendix A for sample problems illustrating these concepts.

PRESCRIPTION WRITING

Define the following abbreviations:

q	every hour
qhs	every night

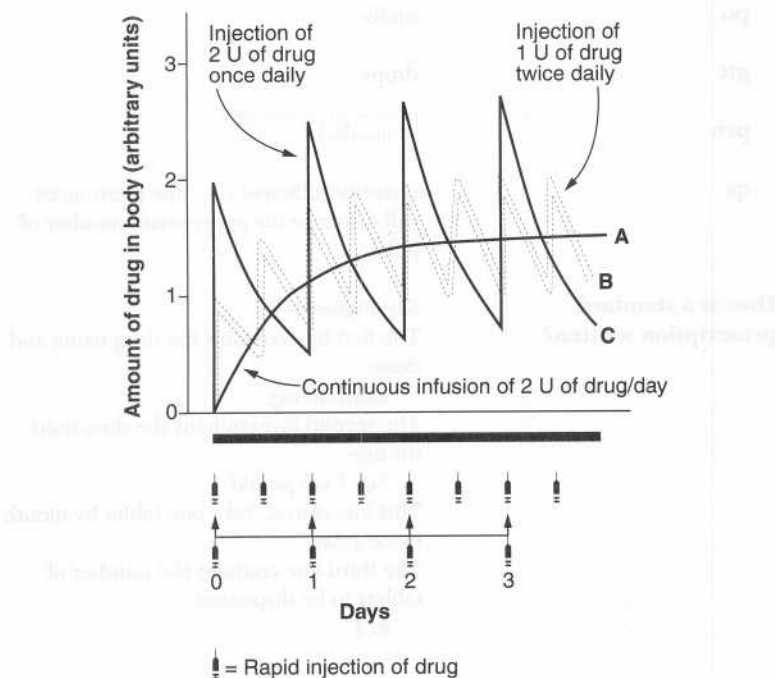


Figure 4-1. Predicted plasma concentration variations of a drug given by infusion (A), twice daily injection (B), or once daily injection (C). Model assumes rapid mixing in a single body compartment and a $t_{1/2}$ of 12 hours. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 20.)

qd	every day
bid	twice a day
tid	three times a day
qid	four times a day
qos	every night at bedtime
stat	immediately
ac	at meal time
hs	at night
pc	after meal time

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po	orally
gtt	drops
prn	as needed
qs	quantity sufficient (i.e., the pharmacist will dispense the appropriate number of pills)

How is a standard prescription written?

See Figure 4-2.

The first line contains the drug name and dose:

Lasix 40 mg

The second line contains the directions for use:

Sig: $\dot{\bar{i}}$ tab po bid

This line states, "take one tablet by mouth twice a day."

The third line contains the number of tablets to be dispensed:

#14

Riverside Hospital
1492 Columbus Ave.
Ashtabula, New York
(212) 613-5000

NAME _____ AGE _____

ADDRESS _____ DATE _____

TELEPHONE NO. _____

R *Lasix 40 mg.*

Sig: $\dot{\bar{i}}$ tab po bid

14

REFILL _____ TIMES _____ PRACTITIONER'S SIGNATURE _____

DEA REG. NO. _____

Figure 4-2. A sample prescription.

Section II

Autonomic Nervous System

Autonomic Nervous System

Section II

5

Introduction to Autonomic Nervous System Pharmacology

Name the two branches of the human nervous system.

1. Central nervous system
2. Peripheral nervous system

What are the two subdivisions of the peripheral nervous system?

1. Somatic nervous system, which innervates skeletal muscle
2. Autonomic nervous system (ANS)

What is the autonomic nervous system?

A collection of nuclei, cell bodies, nerves, ganglia, and plexuses that provides afferent and efferent innervation to smooth muscle and visceral organs of the body

Why is this system important?

The ANS regulates functions that are not under conscious control, such as blood pressure, heart rate, and intestinal motility. (Also, ANS drugs have traditionally been a favorite topic of USMLE examiners.)

What are the two major subdivisions of the ANS?

1. Sympathetic nervous system
2. Parasympathetic nervous system

What are the anatomic differences between these two systems?

The **sympathetic nervous system** originates in the thoracolumbar portion of the spinal cord. The *preganglionic neurons* are short and usually synapse somewhere in the paravertebral ganglia (sympathetic chain). The *postganglionic neurons* are long and terminate at the visceral organs.

The **parasympathetic nervous system** originates from cranial nerve nuclei III, VII, IX, and X, as well as the third

TABLE 5-1. Automatic Nervous System: Sympathetic vs Parasympathetic Responses

Effector Organs ^a	Sympathetic		Parasympathetic	
	Receptor	Response	Receptor	Response
Eye				
Radial muscle (iris)	α_1	Contraction (mydriasis)	—	—
Circular muscle (iris)	—	—	M_3	Contraction (miosis)
Ciliary muscle	β_2	Relaxation	M_3	Contraction (accommodation)
Heart				
SA node	β_1	↑ HR	M_2	↓ HR
AV node	β_1	↑ conduction velocity and automaticity	M_2	↓ conduction velocity
Contractility	β_1	↑ force of contraction (atria & ventricles)	M_2	↓ contractility (atria)
Lung				
Bronchial muscle	β_2	Relaxation (bronchodilation)	M_3	Contraction (bronchoconstriction)
Blood vessels				
Most (except skeletal muscle)	α_1	Constriction	—	—
Skeletal muscle	β_2	Relaxation	—	—
GI (Stomach and Intestine)				
Sphincter	α_1	Constriction (retention)	M_3	Relaxation (defecation)
Motility and tone	α, β_2	↓	M_3	↑ motility and tone

GU				
Urinary sphincter	α_1	Constriction	M_3	Relaxation
Bladder wall	β_2	Relaxation (retention)	M_3	Contraction
Uterus, pregnant	$\alpha_1; \beta_2$	Contraction; relaxation	—	—
Uterus, nonpregnant	β_2	Relaxation	—	—
Penis, seminal vesicles	α_1	Ejaculation	M	Erection
Secretory glands				
Sweat	α_1	Localized secretion	M	Generalized secretion
Intestinal	α_2	Inhibition	M_3	↑ secretion
Bronchial	—	—	M	↑ secretion
Lacrimal	α	↑ secretion (moderate)	M	Profuse secretion
Metabolism				
Adrenal medulla	N_N	Secretion of catecholamines	—	—
Kidney	β_1	↑ renin release	—	—
Skeletal muscle	β_2	Glycogenolysis, ↑ contractility	—	—
Pancreas (beta cells)	α_2	↓ insulin release	—	—
Fat cells	β_3	Lipolysis	—	—

^aThe parasympathetics system controls most organs except blood vessels, which are regulated by the sympathetic nervous system.

N_N = nicotinic; M = muscarinic receptors

(Adapted from Gallia G, Hann CL, Hewson WH: *The Pharmacology Companion*. Ann Arbor, MI, Alert & Oriented Publishing Company, 1997.)

and fourth sacral spinal roots (craniosacral origins). The preganglionic neurons take a long path and synapse onto short postganglionic neurons in or near the target organ.

What are the functions of the sympathetic nervous system?

The sympathetic nervous system is normally active, even at rest; however, it assumes a dominant role when the body becomes stressed in some way. For example, if you sense danger, your heart rate increases, blood pressure rises, eyes dilate, blood sugar rises, bronchioles expand, and blood flow shifts from the skin to skeletal muscles.

The sympathetic nervous system prepares you for **“flight or fight”** situations.



With what major receptors does the sympathetic nervous system work?

Adrenergic receptors—alpha-1 (α_1), alpha-2 (α_2), beta-1 (β_1), beta-2 (β_2), and dopamine receptors (Table 5–1)

What are the actions of the parasympathetic system?

The parasympathetic nervous system is predominant under tranquil conditions. It slows heart rate, lowers blood pressure, increases intestinal activity, constricts the pupils, and empties the urinary bladder.

The parasympathetic nervous system is also known as the **rest and digest** system.



What receptors does the parasympathetic system act upon?

Cholinergic receptors—muscarinic and nicotinic

How are the parasympathetic and sympathetic systems related?

These two systems oppose each other's actions. Remember that both systems are working at all times; however, which system predominates over an organ will depend on the situation. The heart, for example, is predominantly controlled by the parasympathetic system, except under stress, when it is controlled by the sympathetic system.

What are the two principle neurotransmitters in the ANS?

1. Acetylcholine—cholinergic transmission

2. Norepinephrine—adrenergic transmission

Which ion is required for the release of these neurotransmitters from their storage vesicles?

The calcium ion (Ca^{2+}) is required for the release of *most* neurotransmitters from their storage vesicles.

How do autonomic drugs function?

ANS drugs achieve their effects by acting as either agonists or antagonists at cholinergic and adrenergic receptors. The following four chapters discuss each of these drug classes in greater detail.

6

Cholinergic Agonists

What are cholinergic agonists?

Cholinergic agonists are drugs that mimic or potentiate the actions of acetylcholine.

What are the two major families of cholinergic receptors?

1. **Muscarinic**—This receptor family earned its name because it was first identified using muscarine, an alkaloid found in certain poisonous mushrooms.
2. **Nicotinic**

What pharmacologic subtypes of muscarinic receptors exist?

There are several different subtypes of muscarinic receptors, namely, M_1 to M_5 . They are found in ganglia, smooth muscle, myocardium, secretory glands, and the CNS. (For the USMLE, it is not necessary to memorize which subtype of muscarinic receptors a drug will act upon.)

Identify the two types of nicotinic receptors.

1. Neuronal nicotinic (N_N), located in autonomic ganglia
2. Muscular nicotinic (N_M), located in the neuromuscular junction

Where in the body are cholinergic receptors found?

Preganglionic fibers of the autonomic ganglia
 Preganglionic fibers that terminate in the adrenal medulla
 Postganglionic fibers of the parasympathetic system
 Voluntary muscles of the somatic system
 CNS
 Sweat glands innervated by postganglionic sympathetic nervous system
 See Figure 6-1.

What types of cholinergic agonists are available for clinical use?

Cholinergic agonists can be divided into two major groups:

1. **Direct-acting agonists** chemically bind with and activate muscarinic and nicotinic receptors in the body.

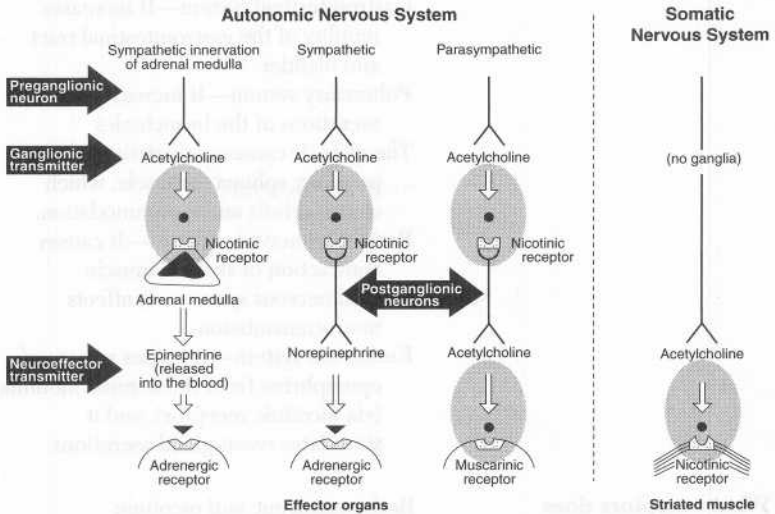


Figure 6-1. Sites of action of cholinergic agonists in the autonomic and somatic nervous systems. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 36.)

2. **Indirect-acting agonists** inhibit the enzyme acetylcholinesterase and therefore increase the concentration of acetylcholine within the synapse.

DIRECT-ACTING AGONISTS

Give six examples of direct-acting agonists.

1. Acetylcholine—prototype
2. Bethanechol
3. Carbachol
4. Pilocarpine
5. Methacholine
6. Nicotine (discussed in *Chapter 17—CNS Stimulants*)

ACETYLCHOLINE

What are the physiologic actions of acetylcholine?

Acetylcholine affects almost every system within the body:

Cardiovascular system—It decreases heart rate, contractility, and blood pressure.

Gastrointestinal system—It increases motility of the gastrointestinal tract and bladder.

Pulmonary system—It increases secretions of the bronchioles

The eye—It causes constriction of the pupillary sphincter muscle, which causes miosis and accommodation.

Peripheral nervous system—It causes contraction of skeletal muscle.

Central nervous system—It affects neurotransmission.

Endocrine system—It causes release of epinephrine from the adrenal medulla (via nicotinic receptor), and it stimulates sweat gland secretions.

What receptors does acetylcholine activate?

Both muscarinic and nicotinic

What are the clinical indications?

Acetylcholine is used to achieve miosis during ophthalmic surgery. In general, it is rarely used because it has widespread effects and is so rapidly hydrolyzed by acetylcholinesterase.

What are the adverse reactions?

The adverse effects result from excessive generalized cholinergic stimulation. They include:

Diarrhea and decreased blood pressure

Urination

Miosis

Bronchoconstriction

Excitation of skeletal muscle

Lacrimation

Salivation and sweating

DUMBELS

NOTE: These adverse effects are typical of *all* direct and indirect cholinergic agonists, not just acetylcholine.



BETHANECHOL (Urecholine)

What type of chemical compound is bethanechol?

A carbamic acid ester

What receptors does it work on? Bethanechol works primarily on muscarinic receptors, but it also has some mild nicotinic properties.

What are its therapeutic uses? Bethanechol increases intestinal motility, especially after surgery. Because this drug also stimulates the detrusor muscle of the bladder, it is also used to treat urinary retention.

BBB—Bethanechol stimulates the Bladder and Bowel.



What are the adverse effects of bethanechol administration? The adverse effects are those that result from generalized cholinergic stimulation (see above).

CARBACHOL

What type of compound is carbachol? A carbamic acid ester similar to bethanechol

State its clinical use. This drug is rarely used in the clinics, but it can be used for glaucoma and to stimulate miosis during ophthalmic surgery.

What receptors does carbachol work on? Both muscarinic and nicotinic receptors

What are its adverse effects? Those that result from excessive generalized cholinergic stimulation

PILOCARPINE (Pilocar)

What type of compound is pilocarpine? An alkaloid

What are pilocarpine's physiologic actions? Causes miosis and contraction of the ciliary muscle
Decreases heart rate
Causes bronchial smooth muscle contraction
Increases secretions from salivary, lacrimal, and sweat glands

Is it cleaved by acetylcholinesterase? No, the drug is unaffected by this enzyme.

State the clinical use. Pilocarpine is extremely good for stimulating miosis and opening the trabecular meshwork around the canal of Schlemm. Therefore, pilocarpine can be used for the treatment of glaucoma.

What receptors does this drug work on? Primarily muscarinic receptors

What are the adverse effects? Unlike the other direct-acting agonists previously discussed, pilocarpine is able to enter the brain and cause CNS disturbances such as hallucinations and convulsions, along with generalized cholinergic stimulation.

METHACHOLINE

What is methacholine used for? Diagnosis of asthma and bronchial hyperreactivity

What receptors does it stimulate? Muscarinic receptors

What are the adverse effects? Generalized cholinergic stimulation

INDIRECT-ACTING AGONISTS

Give six examples of indirect-acting cholinergic agonists.

1. Isoflurophate
2. Echothiophate
3. Parathion
4. Edrophonium
5. Physostigmine
6. Neostigmine

How do they work? By inhibiting the enzyme acetylcholinesterase, which is responsible for the hydrolysis of acetylcholine. Neuronal response to acetylcholine is therefore enhanced.

Which indirect-acting cholinergic agonists have the ability to *irreversibly* inhibit acetylcholinesterase? Only the organophosphates (isoflurophate, echothiophate, and parathion) irreversibly inhibit acetylcholinesterase.

Why are physostigmine, neostigmine, edrophonium, and pyridostigmine considered to be reversible? Because they do not bind covalently to acetylcholinesterase

ORGANOPHOSPHATES (ISOFLUROPHATE, ECHOTHIOPHATE, PARATHION)

Describe the mechanism of action.

Organophosphates bind covalently to acetylcholinesterase and can permanently inactivate the enzyme. The effects of organophosphates can last as long as a week, which is approximately the time needed to synthesize a new molecule of acetylcholinesterase.

Is it at all possible to reverse the effects of organophosphates?

In most cases, no. However, if pralidoxime (a cholinesterase reactivator) is given before the organophosphate binds to acetylcholinesterase and loses one of its alkyl groups (a process called aging), then it may be possible for pralidoxime to remove the organophosphate from acetylcholinesterase (Figure 6-2).

What were these drugs used for in the past?

Organophosphates were used in wars as nerve gases. They produce an immense stimulation at cholinergic receptors throughout the body, causing respiratory muscle paralysis and convulsions.

What are these drugs used for today?

Isoflurophate and echothiophate are used occasionally for glaucoma and accommodative esotropia.

What drug is used to treat organophosphate poisoning?

Atropine is used, along with gastric lavage and charcoal.

What are the toxicities of the organophosphates?

Excessive cholinergic stimulation

PHYSOSTIGMINE

When is physostigmine administered?

For glaucoma—second-choice drug after pilocarpine
 For overdoses of atropine, phenothiazines, and tricyclic antidepressants
 For intestinal and bowel atony
 For accommodative esotropia (rarely)

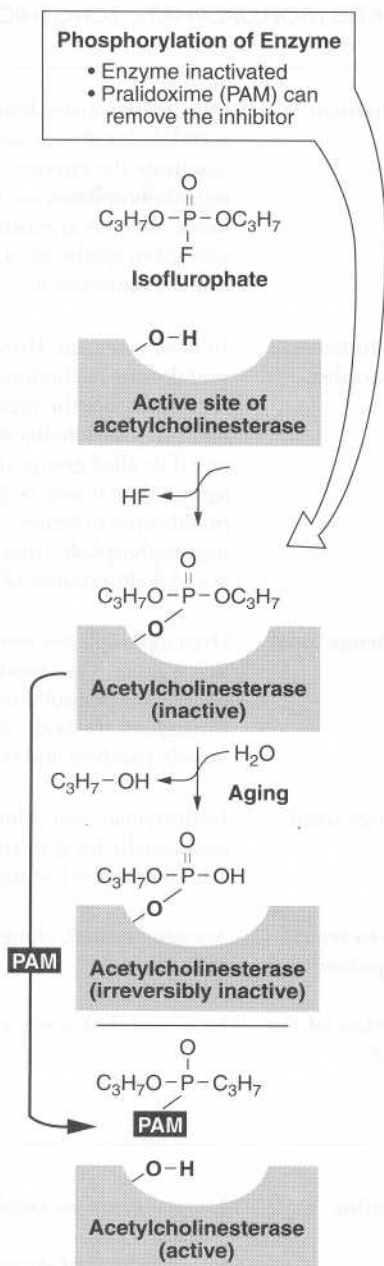


Figure 6-2. Covalent modification of acetylcholinesterase by isoflurophate. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 43.)

Can physostigmine enter the CNS? Yes, because it is a tertiaryamine

State the adverse effects. Convulsions
Muscle paralysis secondary to overstimulation
Cataracts
Generalized excessive cholinergic stimulation

NEOSTIGMINE (Prostigmin)

Does this drug enter the CNS? No, because it is a polar quaternary carbamate

Describe the therapeutic uses. Treatment of myasthenia gravis
Treatment of urinary retention and paralytic ileus
Antidote for nondepolarizing neuromuscular blockade such as with tubocurarine

What is the duration of action? Usually 2 to 4 hours

What are the adverse effects? Excessive cholinergic stimulation

EDROPHONIUM (Enlon)

What is its clinical use? Edrophonium is similar to neostigmine except that it is used in the **diagnosis of myasthenia gravis**. It is not useful for maintenance therapy because of its short duration of action (approximately 5 to 15 minutes). Edrophonium is also used **to differentiate myasthenia gravis from cholinergic crisis**. Both conditions can result in muscle weakness; however, administration of edrophonium helps myasthenia but worsens cholinergic crisis.

What are the adverse effects? Excessive cholinergic stimulation

PYRIDOSTIGMINE (Mestinon)

What is pyridostigmine's duration of action? Very long—usually 3 to 6 hours

What is the clinical use? Because of its long duration of action, pyridostigmine, like neostigmine, can be used for long-term treatment of myasthenia gravis.

What are the adverse effects? Excessive cholinergic stimulation

7

Cholinergic Antagonists

What are cholinergic antagonists?

Drugs that bind to cholinergic receptors (muscarinic and/or nicotinic), but do not trigger the usual intracellular response

Name three subclasses of cholinergic antagonists.

1. Muscarinic blockers
2. Neuromuscular blocking agents—inhibit the efferent impulses to skeletal muscle via the nicotinic muscle receptor (N_M)
3. Ganglionic blockers—inhibit the nicotinic neuronal receptor (N_N) of both parasympathetic and sympathetic ganglia

MUSCARINIC ANTAGONISTS

Give six examples of muscarinic blockers.

1. Atropine (prototype)
2. Scopolamine
3. Homatropine
4. Cyclopentolate
5. Tropicamide
6. Pirenzepine

Are there other drugs that exhibit antimuscarinic properties?

Yes—these include the anti-Parkinson's drugs (e.g., benztropine), the anti-depressants (e.g., Thorazine), antihistamines (e.g., diphenhydramine), and anti-asthmatics (e.g., ipratropium), which are discussed further in later chapters.

ATROPINE

To what family of compounds does atropine belong?

Atropine comes from the plant *Atropa belladonna* and is known as a belladonna alkaloid.

What is the significance of the plant's name?

Belladonna in Latin means **pretty lady**. During the Roman era the plant was used to dilate women's pupils, which was considered to be attractive.

What is atropine's mechanism of action?

It causes **reversible, nonselective** blockade of muscarinic receptors.

What agent can be used to counteract the effects of atropine?

High concentrations of acetylcholine or an equivalent muscarinic agonist

Does this drug cross the blood-brain barrier?

No. Atropine does not readily cross the blood-brain barrier.

What are the pharmacologic actions of atropine?

CNS—At toxic doses can cause restlessness, hallucinations, and delusions

Cardiovascular system—At low doses, atropine reduces heart rate through central stimulation of the vagus nucleus. At high doses, atropine blocks muscarinic receptors of the heart and thus induces tachycardia.

Gastrointestinal system—Reduces salivary gland secretion and GI motility

Pulmonary system—Reduces bronchial secretions and stimulates bronchodilation

Urinary system—Blocks muscarinic receptors in the bladder wall, which results in bladder wall relaxation

Eye—Causes paralysis of the sphincter muscle of the iris and ciliary muscle of the lens, resulting in mydriasis and cycloplegia.

Mydriasis = dilation

Sweat glands—Suppresses sweating, especially in children

You will more readily remember the actions of atropine if you recognize that blocked cholinergic receptors result in an unopposed sympathetic response.



List the therapeutic uses of atropine.

Bradycardia

Mydriasis and cycloplegia—beneficial

When is the use of atropine to effect mydriasis and cycloplegia contraindicated?

when a thorough fundus examination or an accurate refraction is required
Gastrointestinal and bladder spasms
Organophosphate poisoning

How long is atropine's duration of action?

Approximately 4 hours, except when it is placed in the eye, where it usually lasts about 14 days

How is atropine absorbed and excreted?

It is well absorbed from the gastrointestinal system and conjunctival membrane. It is excreted through both hepatic metabolism and renal filtration.

What are the toxic effects of this drug?

Toxic Effect:

Mnemonic:

Dry mouth	"Dry as a bone"
Inhibition of sweating, especially in young children	"Hot as a hare"
Tachycardia and cutaneous vasodilation	"Red as a beet"
Blurring of vision	"Blind as a bat"
Hallucinations and delirium	"Mad as a hatter"



SCOPOLAMINE

What is the classification of scopolamine?

Like atropine, this drug is a belladonna alkaloid.

What is its mechanism of action?

Nonselective competitive blockade of muscarinic receptors

How is scopolamine used therapeutically?

Prevention of motion sickness—"lotion for motion"



How does this drug differ from atropine?

It has a longer duration of action and more potent CNS effects.

What is scopolamine's route of administration?

It is often given transdermally.

Are there any adverse effects?

Yes—similar to those of atropine:
 “Dry as a bone, red as a beet, hot
 as a hare, blind as a bat, mad as a
 hatter.”



HOMATROPINE, CYCLOPENTOLATE (Cyclogyl), AND TROPICAMIDE (Mydracil)

What are these drugs used for?

In ophthalmology, they are given topically for mydriasis and cycloplegia

What are the adverse effects?

Similar to those for atropine but much milder

PIRENZEPINE

What is it?

A selective M_1 muscarinic inhibitor

How is this drug used?

For treating gastric ulcers

What are the adverse effects?

Similar to those for atropine

NEUROMUSCULAR BLOCKING AGENTS

Name the two major sub-divisions of neuromuscular agents.

1. Nondepolarizing blocking agents
2. Depolarizing blocking agents

NONDEPOLARIZING BLOCKING AGENTS

Name four nondepolarizing agents.

1. Tubocurarine—prototype
2. Pancuronium—longer duration of action than tubocurarine
3. Atracurium
4. Vecuronium

What is their mechanism of action?

These drugs competitively block cholinergic transmission at the nicotinic receptors by preventing the binding of acetylcholine to its receptor.

What is the therapeutic use of these agents?

They are used as adjuvant drugs for anesthesia—they promote muscle relaxation.

Are all muscles equally affected?

No. The muscles of the eye and face are affected first, whereas the respiratory muscles are affected last.

- What is the route of administration?** All neuromuscular junction blockers must be given IV because oral absorption is poor.
- What are the adverse effects?** Bronchoconstriction and hypotension, caused by histamine release
- What can be used to counteract the effects of these drugs?** Because neuromuscular junction blockers are competitive inhibitors, their actions can be reversed with edrophonium or neostigmine.

DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

Name the only depolarizing neuromuscular blocking agent used in the United States. Succinylcholine

What is this drug's mechanism of action?

Phase I—Succinylcholine binds to the nicotinic receptor, opens the Na^+ channels, and causes membrane depolarization, which results in transient fasciculations. Flaccid paralysis will follow in a few minutes, because succinylcholine is resistant to acetylcholinesterase and will cause prolonged depolarization of the membrane.

Phase II—Eventually the membrane will at least partially repolarize. However, the receptor is now desensitized to acetylcholine, thus preventing the formation of further action potentials. In other words, succinylcholine is now acting in a manner similar to tubocurarine (Figure 7-1).

What is the duration of action? 3 to 6 minutes if given as a single dose

What substance metabolizes succinylcholine? Plasma cholinesterase

How is succinylcholine used clinically? As an adjuvant to general anesthesia
To facilitate rapid intubation

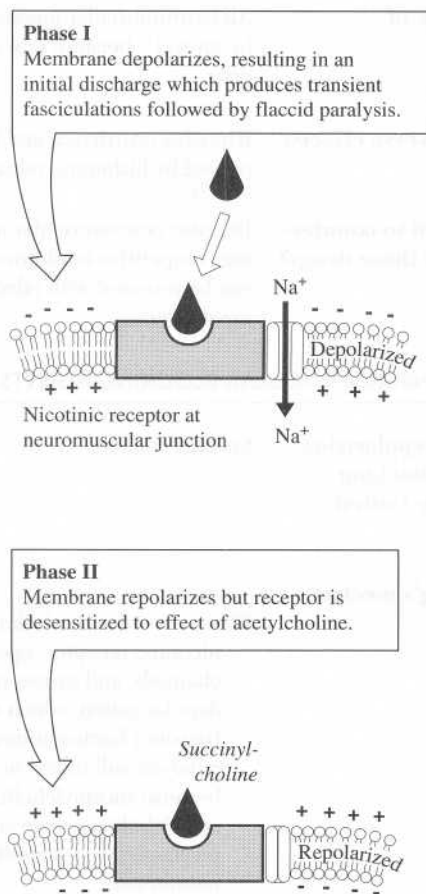


Figure 7-1. Mechanism of action of depolarizing neuromuscular agents. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 53.)

What are the adverse effects? Bronchoconstriction caused by histamine release
Hypotension
Arrhythmias
Apnea due to respiratory paralysis
Malignant hyperthermia

How is malignant hyperthermia treated?

Dantrolene is used. It blocks the release of Ca^{2+} from the sarcoplasmic reticulum, which subsequently reduces skeletal muscle contraction.

Do neuromuscular blocking agents block autonomic ganglia as well?

In general, no. The skeletal muscle end plate and autonomic ganglia use different subtypes of nicotinic receptors. Tubocurarine can, however, produce a small amount of ganglionic blockade.

GANGLIONIC BLOCKERS

Name four ganglionic blockers.

1. Nicotine
2. Hexamethonium
3. Mecamylamine
4. Trimethaphan

What exactly do these drugs do?

Ganglionic inhibitors compete with acetylcholine to bind with nicotinic receptors of both parasympathetic and sympathetic ganglia.

What is the mechanism of action?

Ganglionic blockers can be divided into two groups:

1. Drugs such as nicotine, which initially stimulate the ganglia and then block them because of a persistent depolarization
2. Drugs such as hexamethonium, mecamylamine, and trimethaphan, which block ganglia without any prior stimulation

Describe the physiologic effects.

The physiologic effects of ganglionic blockers can be predicted if you remember which division of the autonomic nervous system exercises dominant control of the organ in question:

Heart—Tachycardia results because the parasympathetic system is normally dominant on the heart.

Arterioles and veins—Vasodilation, increased peripheral blood (sympathetic normally dominant)

Eye—Cycloplegia, mydriasis (parasympathetic normally dominant)

GI system—Reduced motility; diminished gastric and pancreatic secretions (parasympathetic normally dominant)

Urinary system—Urinary retention
(parasympathetic normally dominant)

Sweat glands—Reduced sweating
(sympathetic normally dominant)

What is the therapeutic use? Because they lack selectivity, the ganglionic blockers are very rarely used clinically. In the past, these drugs were used in hypertensive emergencies.

What are the adverse effects? The toxicities of ganglionic blockers are identical to their physiologic effects, which have been described above.

8

Adrenergic Agonists

What are adrenergic agonists?	Drugs or endogenous catecholamines that activate α and/or β receptors. These drugs are also known as sympathomimetics .
How can these substances be classified?	According to mechanism of action (direct vs indirect) as well as receptor site specificity (α_1 , α_2 , β_1 , β_2)
Name the important α selective direct-acting agonists.	Phenylephrine Methoxamine Clonidine Methyldopa
Identify the major β selective direct-acting agonists.	Dobutamine Isoproterenol Albuterol Metaproterenol Terbutaline
List the major α and β direct-acting agonists.	Epinephrine Norepinephrine Dopamine
Which of the direct-acting agonists are considered catecholamines?	Epinephrine, norepinephrine, isoproterenol, dopamine, and dobutamine
Name two indirect-acting adrenergic agonists.	Tyramine and amphetamine
Name two mixed (direct and indirect) agonists.	Ephedrine and metaraminol

DIRECT-ACTING α SELECTIVE RECEPTOR AGONISTS

Where are α_1 and α_2 receptors located?	α_1 receptors are located on the effector organ's postsynaptic membrane. α_2 receptors are predominantly located on the presynaptic membrane.
---	--

Postsynaptic α_2 receptors are limited to the CNS and blood vessels.

What physiologic responses occur when α receptors are stimulated?

α_1 stimulation leads to the release of intracellular calcium from the endoplasmic reticulum via inositol triphosphate (IP_3). This leads to vascular constriction, decreased intestinal tone and motility, contraction of the bladder's internal sphincter, ejaculation, contraction of the pregnant uterus, and mydriasis. (See Table 5-1 in *Chapter 5—Introduction to Autonomic Nervous System Pharmacology*.)

When α_2 presynaptic membrane receptors are stimulated, intracellular cyclic adenosine monophosphate (cAMP) production is inhibited. α_2 receptors function primarily as part of a negative feedback loop. When norepinephrine is released from nerve terminals, some will circulate back to the presynaptic membrane and bind to the α_2 receptor. This will subsequently inhibit further norepinephrine release. Other actions mediated by α_2 receptors include increased vagal tone, platelet aggregation, and suppressed insulin secretion. See Figure 8-1.

Name the direct-acting agonists that are selective for α_1 - and α_2 -adrenergic receptors.

α_1 receptors—phenylephrine and methoxamine
 α_2 receptors—clonidine and methyldopa (discussed in *Chapter 20—Antihypertensive Drugs*)

PHENYLEPHRINE (Neo-Synephrine)

What are phenylephrine's physiologic actions?

Primarily vasoconstriction. The subsequent rise in blood pressure also leads to a reflex bradycardia.

Describe this drug's therapeutic uses.

As a nasal decongestant (primary use)
 To treat hypotension
 For ocular examinations (mydriasis)
 To terminate episodes of paroxysmal atrial tachycardia (PAT)

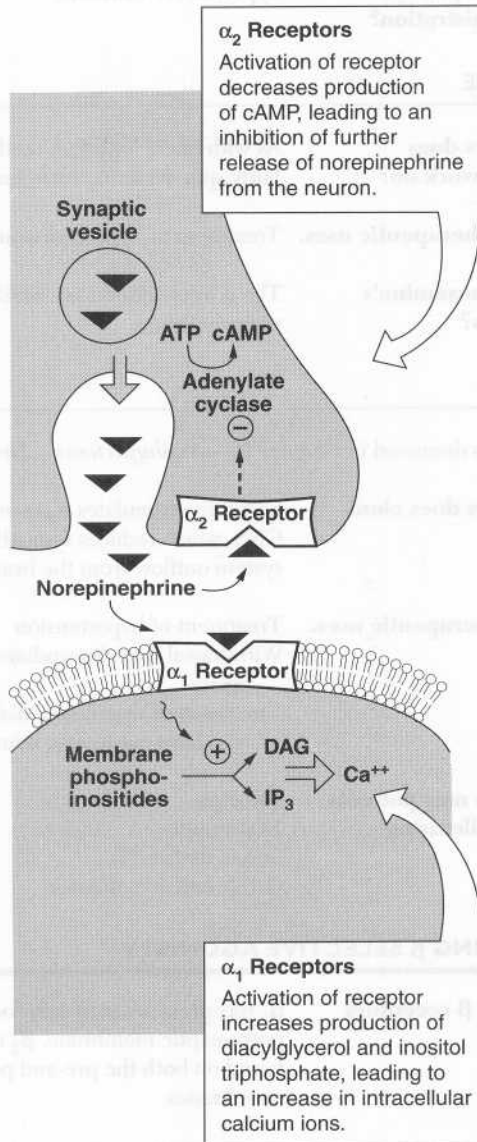


Figure 8-1. Second messengers mediate the effects of α receptors. DAG = diacylglycerol; IP = inositol triphosphate. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 59.)

What are the adverse effects associated with phenylephrine administration? Rebound mucosal swelling and hypertensive headache

METHOXAMINE

What receptors does methoxamine work on? As with phenylephrine, methoxamine is fairly specific for α_1 receptors.

Describe the therapeutic uses. Treatment of hypotension and PAT

What are methoxamine's adverse effects? The adverse effects are similar to those of phenylephrine.

CLONIDINE

Clonidine is also discussed in *Chapter 20—Antihypertensive Drugs*.

What receptors does clonidine work on? Clonidine stimulates α_2 receptors in the CNS, which reduces sympathetic nervous system outflow from the brain.

Describe its therapeutic uses. Treatment of hypertension
Withdrawal from benzodiazepines and opiates
Treatment of diarrhea in diabetic patients who have autonomic neuropathies

What toxicities may patients experience while using clonidine? Sedation
Dry mouth
Sexual dysfunction
Orthostatic hypotension

DIRECT-ACTING β SELECTIVE AGONISTS

Where are the β receptors located? β_1 receptors are primarily located on the postsynaptic membrane. β_2 receptors are found on both the pre- and postsynaptic membranes.

What are the physiologic responses once β receptors are stimulated? β_1 **stimulation** activates adenylate cyclase, which opens calcium channels, leading to cardiac stimulation with both increased inotropic and chronotropic effects. β_1 stimulation also leads to increased lipolysis. β_2 **receptors** work via adenylate cyclase stimulation as well.

In this case, however, bronchial smooth muscle as well as skeletal muscle vasculature are dilated. The uterus, ciliary, and detrusor muscles are relaxed and glucagon release is increased. **Both β_1 and β_2 receptors** produce decreased intestinal tone and motility (just as the α -adrenergic receptors do). See also Table 5-1 in *Chapter 5—Introduction to Autonomic Nervous System Pharmacology*.

DOBUTAMINE

What is it?	A dopamine analogue
What receptors does dobutamine act on?	Primarily β_1 , but it does have some action on β_2 receptors as well
What are the physiologic effects of dobutamine?	Increased heart rate and contractility (β_1) Smooth muscle relaxation (β_2)
What is dobutamine's therapeutic use?	Treatment of unstable CHF and shock
What is the route of administration?	IV
What are this drug's adverse effects?	Arrhythmias Headache Hypertension Palpitations Angina Nausea

ISOPROTERENOL

Which receptors mediate the effects of isoproterenol?	β_1 and β_2 receptors
What are its physiologic actions?	Increases cardiovascular inotropic and chronotropic response (β_1) Lowers peripheral vascular resistance (β_2) Relaxes smooth muscles (β_2)
In what clinical situations is it appropriate to use isoproterenol?	Stimulation of heart rate in patients suffering from heart block and bradycardia In the past, used for treatment of asthma

What is the route of administration? IV

What are the toxicities of isoproterenol? Arrhythmias
Palpitations
Tachycardia
Headache

ALBUTEROL, METAPROTERENOL, AND TERBUTALINE

What are the pharmacologic actions of these β_2 direct-acting agonists? Stimulation of smooth muscle dilatation
Can stimulate β_1 receptors at higher doses

What is the route of administration? Albuterol and metaproterenol are usually inhaled. Terbutaline can be given orally or subcutaneously.

List the therapeutic uses. Treatment of bronchospasm/asthma
Treatment of chronic obstructive pulmonary disease
Treatment of bronchitis
Terbutaline and ritodrine can be used to relax the uterus during premature labor.

What are the potential adverse effects of the β_2 selective drugs? Arrhythmias
Tachycardia
Headache
Nausea and vomiting

DIRECT-ACTING α AND β AGONISTS

EPINEPHRINE

Which receptors does epinephrine act upon? It stimulates α_1 , α_2 , β_1 , and β_2 receptors. At low doses epinephrine stimulates β receptors and at high doses it stimulates α receptors.

What are the physiologic responses to epinephrine? Cardiovascular—increased heart rate and contractility; vasoconstriction of arterioles in the skin, viscera, and mucous membranes
Respiratory—bronchodilation through activation of β_2 receptors
Metabolic—increased glycogenolysis and release of glucagon and a decreased

release of insulin results in
hyperglycemia

What are the therapeutic uses?

Given for bronchospasm secondary to acute asthma or anaphylactic shock
Used in anaphylaxis and cardiac arrest to increase cardiac electrical activity
Used in conjunction with local anesthetics to prolong effects via vasoconstriction
Used to achieve hemostasis

What are epinephrine's adverse effects?

Cardiac arrhythmias
Hypertension
Palpitations
Dizziness, anxiety, headache
Tremor
Myocardial infarction due to increased cardiac work
Pulmonary edema

To what does the term "epinephrine reversal" refer?

When epinephrine is administered alone, it will cause an increase in systemic blood pressure because of its α activity. When given in conjunction with an α blocker such as phenoxybenzamine, epinephrine will cause a decrease in blood pressure because of its β_2 activity. This effect is known as epinephrine reversal.

NOREPINEPHRINE (Levophed)

What receptors does norepinephrine stimulate?

α_1 , α_2 , and β_1 receptors. Norepinephrine has a stronger affinity for α receptors than for β receptors.

What are its physiologic effects?

Vasoconstriction
Reflex bradycardia

What is its therapeutic use?

It is one of the last-line agents in the treatment of shock.

What are norepinephrine's adverse effects?

Tissue hypoxia secondary to potent vasoconstriction
Decreased perfusion to the kidneys
Tissue necrosis due to extravasation during intravenous administration
Arrhythmias

DOPAMINE

Where is this agonist found?	It is synthesized in the CNS, sympathetic ganglia, and adrenal medulla.
What receptors does dopamine act on?	α_1 , β_1 , and β_2 . It also stimulates its own dopamine (D_1 and D_2) receptors located in the peripheral mesenteric and renal vascular beds. Dopamine receptors are stimulated at low dose, β receptors at moderate dose, and α_1 receptors at higher doses. Dopamine does not cross the blood-brain barrier.
What are dopamine's therapeutic uses?	Treatment of shock—it raises blood pressure by stimulating the β_1 receptors of the heart Used in acute renal failure to increase renal blood flow Treatment of acute congestive heart failure
How is it administered?	IV
What are dopamine's adverse effects?	Decreased renal perfusion at higher doses Arrhythmias Tachycardia Hypertension Tissue necrosis can occur if dopamine extravasates during infusion.

INDIRECT-ACTING AGONISTS

TYRAMINE

What is tyramine?	Tyramine is a by-product of tyrosine metabolism; tyrosine is a precursor to dopamine, epinephrine, and norepinephrine.
What is the mechanism of action of tyramine?	Tyramine is taken up by sympathetic neurons, which causes a release of catecholamines.
Is there a therapeutic use for tyramine?	No

What are tyramine's adverse effects?

It can cause a **hypertensive emergency** in patients who take MAO inhibiting drugs since MAO is responsible for the metabolism of tyramine. It is important to **warn patients who are taking MAO inhibitors** not to eat foods with high tyramine concentrations, such as red wine, beer, chocolate, and cheese.

AMPHETAMINE

What are its pharmacologic actions?

It releases stores of norepinephrine and dopamine. It can enter the CNS.

When is it appropriate to administer amphetamine?

Amphetamine is used to treat attention deficit hyperactivity disorder (ADHD) and narcolepsy. It is also used for appetite suppression.

What are the adverse effects?

Psychological and physical dependence
Psychosis
Confusion
Insomnia
Headache
Restlessness
Palpitations
Tachycardia
Impotence

MIXED (DIRECT AND INDIRECT) AGONISTS

EPHEDRINE

How does ephedrine work?

It stimulates the release of norepinephrine from nerve terminals. It also acts as a direct adrenergic agonist.

What are ephedrine's therapeutic uses?

Ephedrine is used in the treatment of urinary incontinence, bronchospasm, and hypotension.

What are the adverse effects?

Arrhythmias
Palpitations
Insomnia
Hypertension

METARAMINOL

Describe this drug's actions. Metaraminol acts indirectly by releasing norepinephrine. It can also directly stimulate α receptors.

What are its therapeutic uses? Treatment of hypotension and termination of PAT episodes

What are the adverse effects? Similar to those of norepinephrine

9

Adrenergic Antagonists

What are adrenergic antagonists?

They are drugs that bind to adrenergic receptors but do not initiate the usual intracellular response.

Name the two major subdivisions of this drug class.

1. α blockers
2. β blockers

Is there another class of adrenergic antagonists?

Yes—the indirect adrenergic antagonists

α BLOCKERS

Name six α blockers.

1. Prazosin (Minipress)— α_1 -adrenergic selective, reversible
2. Doxazosin (Cardura)— α_1 -adrenergic selective, reversible
3. Terazosin (Hytrin)— α_1 -adrenergic selective, reversible
4. Phenoxybenzamine (Dibenzylamine)—nonselective, **irreversible**
—Remember, **phenoxybenzamine** is the only α -adrenergic receptor mentioned that is nonreversible (📌 board question)
5. Yohimbine (Yocon)— α_2 -adrenergic selective, reversible
6. Phentolamine (Regitine)—nonselective, reversible

PRAZOSIN, TERAZOSIN, AND DOXAZOSIN

What is their mechanism of action?

They competitively and selectively block α_1 -adrenergic receptors.

Describe the physiologic sequelae of α_1 blockade.

Blockade of α_1 -adrenergic receptors on vascular smooth muscle inhibits constriction of arterioles and veins. This results in decreased peripheral vascular resistance and a lower blood pressure.

Blockade of α_1 -adrenergic receptors in bladder smooth muscle results in relaxation and decreased resistance to urine flow.

What are the clinical uses?

Treatment of hypertension
Prevention of urinary retention in patients who have benign prostatic hypertrophy

Are there adverse effects?

Prazosin and structural analogues can cause:
Gastrointestinal hypermotility
Orthostatic hypertension, especially after the initial dose
Sexual dysfunction, dry mouth, and dizziness

PHENOXYBENZAMINE

How does this drug work?

Phenoxybenzamine is unique in that it works by noncompetitively blocking the α_1 postsynaptic receptor and α_2 presynaptic receptors.

Describe the physiologic actions of phenoxybenzamine.

It blocks peripheral vasoconstriction. It induces a reflex tachycardia.

How is phenoxybenzamine administered?

Orally

What is the duration of action?

Because it binds covalently to the receptor, this drug has a very long duration of action (approximately 14–48 hours).

Describe the therapeutic use.

Treatment of patients with pheochromocytoma-induced hypertension. Phenoxybenzamine is very effective because of its long duration of action.
Treatment of patients with benign prostatic hypertrophy. Phenoxybenzamine reduces the size of the prostate.
Treatment of patients with spinal cord injuries who may suffer from hyperreflexia, which results in high blood pressure. Phenoxybenzamine blunts this response.

What are the toxicities associated with the use of phenoxylbenzamine?

Treatment of patients with Raynaud's disease

Orthostatic hypotension

Reflex tachycardia—If severe, it may induce anginal pain; therefore phenoxylbenzamine is contraindicated in patients with coronary disease.

Inhibition of ejaculation due to lack of smooth muscle contraction in the vas deferens

YOHIMBINE

What is it?

A selective α_2 -receptor antagonist

Describe the clinical use.

It is sometimes used to treat impotency via direct penile injection.

PHENTOLAMINE

What is it?

An imidazole derivative

Describe the mechanism of action.

Reversibly blocks α_1 and α_2 receptors

How is this drug used clinically?

Because it has a half-life of only 4 hours, phentolamine is used for the short-term control of pheochromocytoma-induced hypertension.

What is the route of administration?

IV or IM—poorly absorbed orally

What are the adverse effects of phentolamine administration?

Orthostatic hypotension

Gastrointestinal stimulation which may lead to peptic ulcers

Tachycardia, myocardial infarction, or arrhythmias due to reflex sympathetic response

β BLOCKERS

How are β blockers subclassified?

All of the β blockers are competitive antagonists; however, they can be subgrouped according to three major properties:

1. Selectivity of receptor blockade

2. Possession of intrinsic sympathomimetic activity
3. Capacity to block α -adrenergic receptors

β_1 SELECTIVE BLOCKERS

Name four selective β_1 blockers.

1. Atenolol (Tenormin)
2. Esmolol (Brevibloc)
3. Acebutolol (Sectral)
4. Metoprolol (Lopressor)

In general, β -blockers starting with A or M are cardioselective.

Is their β_1 selectivity absolute?

No. At high doses these drugs will block β_2 receptors.

What is the main advantage of β_1 selectivity?

These drugs are sometimes called cardioselective because they lack the unwanted bronchoconstrictor and hypoglycemic effects of nonselective blockers.

What clinical conditions warrant the use of cardioselective β blockers?

Atenolol—Hypertension, myocardial infarction

Esmolol—Because of its very short duration of action (10 minutes), it is used when immediate β blockade is needed, such as for thyroid storm. It is only administered IV.

Acebutolol—Hypertension

Metoprolol—Hypertension, anginal pain, myocardial infarction

NONSELECTIVE β -ADRENERGIC ANTAGONISTS

What is the prototype nonselective β blocker?

Propranolol

Name the pharmacologic actions of nonselective β blockers.

Decreased cardiac output and blood pressure

Reduction of sinus rate and conduction through the atria

Peripheral vasoconstriction

Bronchoconstriction—Remember, the cardioselective β_1 blockers lack the bronchoconstrictive and hypoglycemic effects of nonselective blockers.

Decreased glycogenolysis and glucagon secretion

Increased VLDL and decreased HDL

How is propranolol absorbed?	This drug is almost completely absorbed after oral administration, but only approximately 25% reaches the systemic circulation because of first-pass metabolism.
What is the site of propranolol's metabolism?	The liver
In what clinical situations are nonselective β blockers indicated?	Hypertension Angina, tachycardia Arrhythmia Thyroid storm Acute panic syndrome Migraine headaches
Name two other nonselective β-adrenergic antagonists.	Timolol and nadolol—They have extremely long half-lives (20 hours).
What is the clinical use of these two drugs?	Treatment of glaucoma—They decrease the production of aqueous humor by the ciliary body.
What are the adverse effects of nonselective β blockers?	Bradycardia Bronchoconstriction—can result in an asthmatic attack May hide warning signs of hypoglycemia such as tachycardia; therefore, it is critical to monitor diabetics who are receiving β -blockers. Fatigue Depression Sexual dysfunction

β BLOCKERS WITH INTRINSIC SYMPATHOMIMETIC ACTIVITY

Name two drugs that are classified as β blockers but also have some β-agonistic properties.	Acebutolol and pindolol
Why are these drugs considered to be partial agonists?	They very mildly stimulate both β_1 - and β_2 -adrenergic receptors. However, their intrinsic effects are not as strong as that of a full agonist, such as isoproterenol.
What are these two drugs used for?	Treatment of hypertension in patients prone to bradycardia
Are there any advantages to using these agents?	Acebutolol and pindolol produce bronchoconstriction only at extremely

high doses. They do not induce bradycardia to the degree that full antagonists do, and they cause very minimal disruption of lipid and carbohydrate metabolism.

β BLOCKERS WITH α BLOCKING CAPACITY

Labetalol

What is this drug's mechanism of action? Nonselective β -blockade along with α_1 -adrenergic selective blockade, which results in peripheral vasodilation rather than the vasoconstriction that occurs with the other β blockers

What is the clinical use? Treatment of hypertension and atrial fibrillation

What are the adverse effects? Orthostatic hypotension and dizziness

Carvedilol (Coreg)

What is it? A β blocker that also has α_1 -blocking properties

List the clinical uses. Treatment of hypertension
Treatment of chronic CHF—Although it may seem paradoxical to use β blockers in the treatment of CHF, since they can also worsen symptoms, they appear to benefit the patient by reducing sympathetic activity. They may also improve diastolic dysfunction by prolonging diastolic filling time.

What are the mechanisms of action? Reduction of sympathetic activity
Improvement of diastolic dysfunction by prolonging diastolic filling time

What are the contraindications to use? β blockers are contraindicated in the treatment of acute CHF. They are only used when the patient is hemodynamically stable

β_2 SELECTIVE BLOCKERS

Butoxamine

What is it? A selective β_2 -adrenergic antagonist

Does this drug have any clinical use? No, not currently

NEW β -BLOCKING DRUGS

Are there many other β blockers?	Yes. New β blockers are produced yearly.
How do these new drugs differ from the β blockers discussed here?	Primarily in their pharmacokinetics
How can physicians recognize these new drugs?	By the -olol ending in their names
What are the indications and adverse effects of the new β blockers?	Generally they will be similar to those of other β blockers.

INDIRECT ADRENERGIC ANTAGONISTS

Why are guanethidine and reserpine considered indirect adrenergic antagonists?	They do not directly block α - or β -adrenergic receptors. They do, however, block the release of norepinephrine from nerve endings—in effect, they antagonize the effects of the sympathetic system.
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GUANETHIDINE (ISMELIN)

What is this drug's mechanism of action?	It enters the peripheral adrenergic nerve by a reuptake mechanism for norepinephrine and binds to storage vesicles, the action of which subsequently blocks the release of stored norepinephrine.
Does guanethidine have a clinical use?	Yes—treatment of hypertension
What are the adverse effects?	Orthostatic hypotension and sexual dysfunction

RESERPINE

What is it?	A <i>Rauwolfia</i> alkaloid
What is reserpine's mechanism of action?	It blocks norepinephrine transport from cytoplasm into intracellular storage vesicles. Subsequently, the neuron is not able to release any catecholamines.
How is this drug used clinically?	For treating hypertension (very rarely used)
What are the adverse effects?	CNS depression and bradycardia

Section III

Central Nervous System

Section III

Central Nervous System

10

Introduction to Central Nervous System Pharmacology

Name the major CNS neurotransmitters.

Acetylcholine
Norepinephrine
Dopamine
Serotonin
Gamma-aminobutyric acid (GABA) and glycine—neutral amino acids
Glutamate/aspartate—acidic amino acids

What types of receptors are most commonly found in the CNS?

Ion-gated receptors (Na^+ , K^+ , Cl^- , Ca^{2+})

What are the primary functions of a neurotransmitter?

To bind a receptor and subsequently either excite or inhibit the postsynaptic neuron

What are EPSPs?

Excitatory postsynaptic potentials—initiated when an excitatory neurotransmitter activates Na or Ca channels

Give five examples of excitatory neurotransmitters.

1. Norepinephrine
2. Dopamine
3. Acetylcholine
4. Glutamate
5. Aspartate

What are IPSPs?

Inhibitory postsynaptic potentials—initiated when an inhibitory neurotransmitter opens chloride channels and the cell membrane becomes hyperpolarized. IPSPs make it more difficult for the neuron to become activated (Figure 10-1).

Give two examples of inhibitory neurotransmitters.

1. Glycine
2. GABA

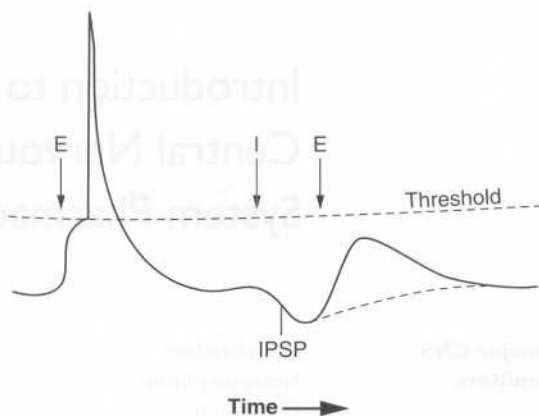


Figure 10-1. Interaction of excitatory and inhibitory synapses. On the left, a suprathreshold stimulus is given to an excitatory pathway (E). On the right, this same stimulus is given shortly after stimulating an inhibitory pathway (I), which prevents the excitatory potential from reaching threshold. (Redrawn from Katzung BG: *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT, Appleton & Lange, 1998, p 345.)

In general, how do drugs affecting the CNS work?

Most drugs will affect production, storage, release, or metabolism of a neurotransmitter. Other agents may affect the postsynaptic receptor.

What are the major differences between the autonomic nervous system and the central nervous system?

There are three major differences:

1. The number of neurotransmitters is greater in the CNS.
2. The number of synapses is greater in the CNS.
3. The CNS, unlike the autonomic nervous system, has a large array of inhibitory neurons that serve to modulate action.

11

Anxiolytics, Hypnotics, and Sedatives

Define anxiety.

An unpleasant emotional state consisting of apprehension, tension, and feelings of danger, without a real or logical cause

What are some of the physical symptoms seen with anxiety?

Tachycardia
Tachypnea
Sweating
Trembling
Weakness

What are the major classes of drugs used to treat anxiety?

Benzodiazepines—the most frequently used drugs for anxiety
Azaspirones—for example, buspirone
Carbamates—for example, meprobamate
Barbiturates—rarely used today because of severe side effects and a low therapeutic index. These drugs have generally been replaced by the benzodiazepines.

BENZODIAZEPINES

Give some examples of benzodiazepines and their approximate duration of action.

Short-Acting (2–8 hours):

Oxazepam (Serax)
Clonazepam (Klonopin)
Midazolam (Versed)
Triazolam (Halcion)

Intermediate-Acting (10–20 hours):

Temazepam (Restoril)
Lorazepam (Ativan)
Alprazolam (Xanax)

Long-Acting(1–3 days):

Chlordiazepoxide(Librium)

Diazepam (Valium)

Flurazepam (Dalmane)

What is GABA?

GABA (γ -aminobutyric acid) is the major inhibitory neurotransmitter of the CNS.

How do benzodiazepines work?

When benzodiazepines bind to specific receptors that are separate from but adjacent to the GABA_A receptor, they potentiate the binding of GABA to its own receptor. The binding of GABA to its own receptor results in increased chloride ion conductance, cell membrane hyperpolarization, and decreased initiation of action potentials. Remember that benzodiazepines do not bind to GABA receptors—they bind adjacent to them (Figure 11–1).

What are the therapeutic indications for benzodiazepines?

These drugs are used clinically as muscle relaxants and in the treatment of the following:

Anxiety disorders

Panic disorders—alprazolam is the drug of choice

Status epilepticus—diazepam is the drug of choice

Sleep disorders

Insomnia—All benzodiazepines can be sedating, but lorazepam and temazepam are the most commonly used.

Alcohol withdrawal—diazepam most commonly used

What is their route of administration?

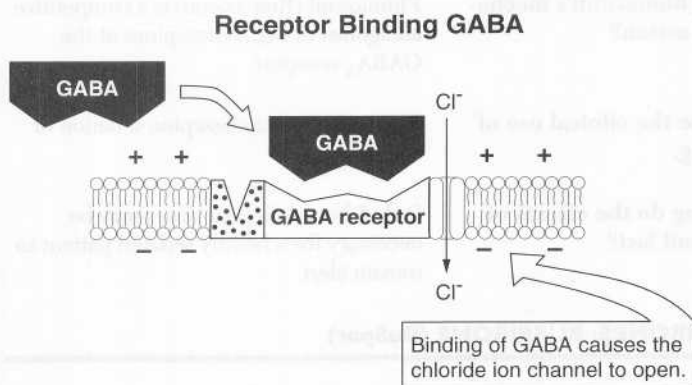
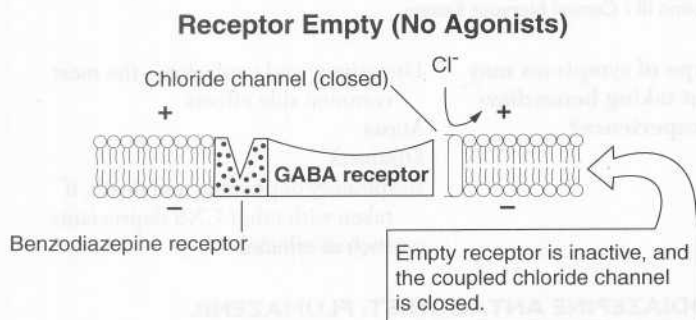
PO, IV, or IM

Where are benzodiazepines metabolized?

They are metabolized in the liver and excreted in urine. Many of the benzodiazepines have active metabolites.

Does dependence occur?

Yes. Prolonged use can result in dependence. Abrupt discontinuation can result in withdrawal symptoms, including confusion, anxiety, and agitation.



Receptor Binding GABA and Benzodiazepine

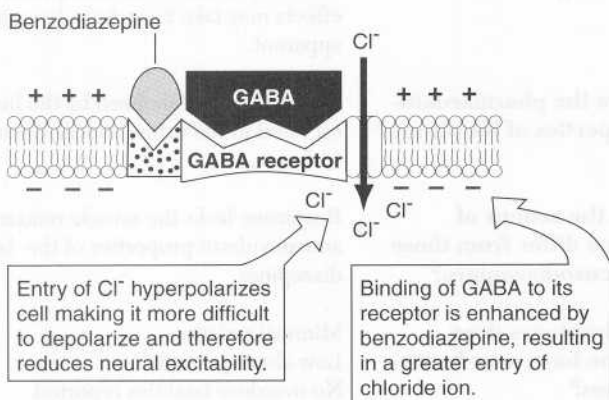


Figure 11-1. Schematic diagram of benzodiazepine-GABA-chloride ion channel complex. GABA = γ -aminobutyric acid. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 91.)

What type of symptoms may a patient taking benzodiazepines experience?

Drowsiness and confusion—the most common side effects
Ataxia
Dizziness
Respiratory depression and death, if taken with other CNS depressants such as ethanol

BENZODIAZEPINE ANTAGONIST: FLUMAZENIL (ROMAZICON)

What is flumazenil's mechanism of action?

Flumazenil (Romazicon) is a competitive antagonist of benzodiazepines at the GABA_A receptor.

Describe the clinical use of this drug.

Reversal of benzodiazepine sedation or overdose

How long do the effects of flumazenil last?

Only 1 hour—Repeat doses may be necessary for a heavily sedated patient to remain alert.

AZASPIRONES: BUSPIRONE (BuSpar)

How does buspirone work?

It acts as a partial agonist at serotonin (5-HT_{1A}) receptors.

What are the indications for this drug?

Buspirone is used for generalized anxiety; however, unlike benzodiazepines, its effects may take 2 weeks to become apparent.

What are the pharmacokinetic properties of buspirone?

This drug is metabolized by the liver and excreted in the urine; its half-life is 2 to 11 hours.

How do the actions of buspirone differ from those of the benzodiazepines?

Buspirone lacks the muscle relaxant and anticonvulsant properties of the benzodiazepines.

What advantages does buspirone have over benzodiazepines?

Minimal sedation
Low abuse potential
No overdose fatalities reported
No withdrawal symptoms

What toxic effects are associated with buspirone?

Headache, nausea, dizziness

CARBAMATES: MEPROBAMATE

What is meprobamate's mechanism of action?	It is not well known.
What is the clinical use?	It is now virtually obsolete. In the past it was used primarily in the treatment of anxiety.
What are the adverse effects?	Respiratory depression—major toxic effect Hypotension Shock Heart failure

BARBITURATES

Give four examples of barbiturates.	<ol style="list-style-type: none"> 1. Phenobarbital (Luminal)—long-acting 2. Pentobarbital (Nembutal)—short-acting 3. Amobarbital (Amytal)—short-acting 4. Thiopental (Pentothal)—ultrashort-acting
How do these drugs work?	Like benzodiazepines, barbiturates facilitate GABA action on chloride entry into the cell, which results in membrane hyperpolarization and a decrease in neuron excitability. Barbiturates do not, however, bind to benzodiazepine receptors.
What are the therapeutic indications for barbiturate administration?	Induction of anesthesia—thiopental Anticonvulsants—e.g., phenobarbital Treatment of anxiety Induction of hypnosis
Why are benzodiazepines favored over barbiturates for the treatment of anxiety?	Benzodiazepines have a much higher therapeutic index than do barbiturates (Figure 11-2).
By what routes can barbiturates be administered?	IV, PO, or IM
What are the pharmacokinetic properties of barbiturates?	They are metabolized in the liver and excreted in the urine.

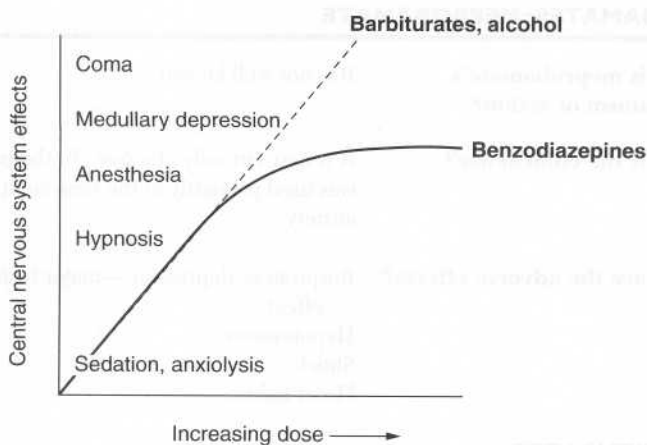


Figure 11-2. Comparison of dose-response relationships of benzodiazepines and barbiturates. (Redrawn from Gallia G, Hann CL, Hewson WH: *The Pharmacology Companion*. Alert & Oriented Publishing Company, 1997, p 33, Fig 3.1.)

What determines the duration of action of thio-pental?

Redistribution to the other tissues

Does barbiturate dependency occur?

Yes—abrupt cessation can lead to severe withdrawal symptoms (tremor, restlessness, nausea, seizures, and cardiac arrest).

For whom are barbiturates contraindicated?

For patients who have acute intermittent porphyria, because they increase porphyrin synthesis

What are the adverse effects of these drugs?

Drowsiness and decreased motor control
Induction of the P-450 system
Addiction
Respiratory depression and coma in high doses
Allergic reactions, especially in patients with asthma

OTHER SEDATIVES

ZOLPIDEM (Ambien)

Describe this drug's clinical use.

Treatment of insomnia

What are its adverse effects? Ataxia and confusion

CHLORAL HYDRATE

What are its clinical uses? Hypnosis
Sedation (in children)

Describe this drug's adverse effects. Gastrointestinal distress
Unpleasant taste

12

Antipsychotics

What are antipsychotic drugs?

Antipsychotics, also known as neuroleptics, are drugs used primarily to treat psychotic states such as schizophrenia, delusional disorder, and other hallucinatory states.

What is their mechanism of action?

Antipsychotics block various receptors including cholinergic, adrenergic, serotonergic, muscarinic, and histamine receptors. However, their antipsychotic actions are thought to be due to blocking of **dopamine receptors** in the central nervous system, particularly the D_2 receptors in the mesocortical and mesolimbic systems of the brain.

Do antipsychotic agents differ in potency?

Yes—a drug's potency parallels its affinity for D_2 receptors. Haloperidol and thiothixene are high-potency drugs because they have high affinity for the D_2 receptors, whereas chlorpromazine and thioridazine are low-potency drugs because they have low affinity for D_2 receptors.

Do antipsychotics differ in efficacy?

No! The traditional antipsychotics are all considered to be equivalent in efficacy.

How are antipsychotics usually administered?

In most cases these drugs are given orally; they can be given intramuscularly if the patient is noncompliant.

Describe the absorption and metabolism of the traditional antipsychotics.

They are variably absorbed orally but they pass into the brain easily and have a large volume of distribution. Metabolism occurs by the cytochrome P-450 system in the liver.

What is the onset of action?

Antipsychotics may not become effective for several weeks. However, sedation and other side effects can occur rapidly.

Can these drugs cure illnesses such as schizophrenia?

No! Antipsychotics only reduce the symptoms of the illness; they cannot cure the illness.

How are the antipsychotics classified?

Classification is based on structural differences. The major classes include phenothiazines, butyrophenones, dibenzoxazepines, thioxanthenes, and benzisoxazoles.

TRADITIONAL ANTIPSYCHOTICS

PHENOTHIAZINES

What are some examples of phenothiazines?

Chlorpromazine (Thorazine)—prototype
Fluphenazine (Prolixin)
Trifluoperazine (Stelazine)
Thioridazine (Mellaril)
Perphenazine (Trilafon)

What distinctive side effects does thioridazine cause?

Pigmentary retinopathy
May cause cardiac arrhythmias and conduction block

BUTYROPHENONES

Name two drugs in this class.

Haloperidol (Haldol)
Droperidol (Inapsine)

Other than psychotic states, for what can haloperidol be used?

Tourette's syndrome
Huntington's disease
Phencyclidine overdose—drug of choice

What type of side effect is especially pronounced with haloperidol?

Extrapyramidal side effects (common board question)

DIBENZOXAZEPINES

Name a drug that belongs to this class.

Loxapine (Loxitane)

THIOXANTHENES

Name a drug that belongs to this class.

Thiothixene (Navane)

CLINICAL USES AND SIDE EFFECTS

What are the clinical applications of traditional anti-psychotic agents?

Traditional neuroleptics have several therapeutic uses, but the most important to remember are:

Treatment of any agitated or psychotic state, such as bipolar disease or schizophrenia (These agents are especially effective for the positive symptoms of schizophrenia, such as delusions, thought disorders, and hallucinations.)

Antiemetic therapy due to blockade of dopamine in the chemoreceptor trigger zone (Thioridazine, however, cannot be used for this purpose.)

Treatment of Tourette's syndrome—haloperidol

Treatment of intractable hiccups—chlorpromazine

Antipruritic therapy—promethazine (because of histamine blockade)

What's an easy way to remember the side effects of the traditional antipsychotics?

With a few exceptions, all of the traditional antipsychotics have similar toxicities—namely, sedation, extrapyramidal effects, anticholinergic effects, and α -adrenergic effects (hypotension).

Do all traditional antipsychotics produce the same degree of each type of side effect?

No. The severity of each adverse effect varies among the classes of antipsychotic drugs. For example, high-potency drugs such as haloperidol and fluphenazine produce the greatest extrapyramidal effects, and low-potency drugs such as thioridazine and chlorpromazine produce the highest anticholinergic effects (Table 12-1).


Describe the toxicities of traditional antipsychotic agents.

CNS sedation—seen markedly with the phenothiazines

Endocrine alteration—galactorrhea, amenorrhea, and infertility, likely due to blockade of dopamine release from the pituitary

Anticholinergic effects—dry mouth, constipation, urinary retention, and blurry vision

Table 12–1. Neuroleptic Drug Side-Effect Profiles

Potency	Drug	Side Effects			
		Sedation	Extrapyramidal Effects	Anticholinergic Effects	α -Adrenergic Effects
HIGH 	Haloperidol	1	4	1	1
	Fluphenazine	1	4	2	1
	Thiothixene	2	3	2	1
	Trifluoperazine	2	3	2	1
	Loxapine	2	2	2	2
	Chlorpromazine	4	2	3	4
LOW	Thioridazine	4	1	4	4

*1 = low, 4 = high

Antiadrenergic effects—watch for light-headedness and orthostatic hypotension secondary to α -adrenergic blockade. Phenothiazines can cause failure to ejaculate.

Extrapyramidal side effects—akathisia (motor restlessness), parkinsonian syndrome (bradykinic rigidity, tremor), acute dystonic reactions (slow, prolonged muscle spasms of tongue, neck, face), neuroleptic malignant syndrome, and tardive dyskinesia (common board question)

What is tardive dyskinesia?

Tardive dyskinesia is a symptom that may occur after prolonged therapy with neuroleptics (6 months to 1 year). It is characterized by rhythmical involuntary movements of the tongue, lips, or jaw. Patients may also demonstrate puckering of the mouth, or even chewing movements.

Is tardive dyskinesia reversible?

There is no known treatment for established cases of tardive dyskinesia. The syndrome may remit partially or completely if neuroleptic treatment is withdrawn, although in many cases it is irreversible. Anticholinergic agents actually increase the severity of tardive dyskinesia.

What is neuroleptic malignant syndrome?

Patients who receive neuroleptics for long-term treatment may experience rigidity, altered mental status, cardiac arrhythmias, hypertension, and life-threatening hyperpyrexia.

What is the therapy for neuroleptic malignant syndrome?

This disorder is treated with dantrolene, a skeletal muscle relaxant (common board question).

ATYPICAL ANTIPSYCHOTIC DRUGS

Name three examples of atypical antipsychotic drugs.

1. Clozapine (Clozaril)
2. Risperidone (Risperdal)
3. Olanzapine (Zyprexa)

Why are these drugs considered “atypical”?

In addition to blocking dopamine receptors, atypical antipsychotics also produce significant blockade on serotonin (5-HT) receptors. They also are rarely associated with extrapyramidal side effects.

Describe the actions of clozapine.

This agent is a dibenzodiazepine derivative. It differs from traditional antipsychotics in its potent blockade of serotonin (5-HT₂) receptors along with the usual dopamine blockade.

What is it used for?

Clozapine has been effective in treating cases of schizophrenia that are refractory to other neuroleptic drugs. It is especially effective in treating the negative symptoms of schizophrenia (blunted emotion, withdrawal, reduced ability to form relationships).

What are the side effects?

Clozapine causes fewer extrapyramidal side effects than traditional neuroleptics. Clozapine does cause seizures and a very dangerous agranulocytosis in 1% to 2% of patients (common board question). Weekly blood tests are required for patients receiving clozapine therapy.

Describe the actions of risperidone.

Risperidone (Risperdal) is a benzisoxazole drug that, like clozapine, has a very high affinity for 5-HT₂ receptors. It also has antidopaminergic (D₂) activity. However, risperidone exhibits no anticholinergic effects and diminished extrapyramidal effects. Risperidone is a first-line agent for the treatment of schizophrenia since it is effective for both the positive and negative symptoms of the disease. The drug is also known to prolong QT intervals and therefore should be used with caution in patients who have abnormal QT intervals.

Describe the actions of olanzapine.

Like risperidone and clozapine, olanzapine blocks both dopamine and serotonin receptors. Effective in the treatment of schizophrenia, it can produce anticholinergic effects as well as sedation and orthostatic hypotension.

13

Drugs Used to Treat Depression and Mania

ANTIDEPRESSANTS

What is depression?

An affective symptom characterized by intense sadness, general loss of interest in the everyday aspects of life, insomnia, changes in appetite, and low self-esteem.

What does the biogenic amine theory of depression propose?

That depression is due to a deficiency of norepinephrine, serotonin, and dopamine in the synapses of the CNS.

List the major categories of antidepressants.

Tricyclics
Serotonin-specific reuptake inhibitors (SSRIs)
Monamine oxidase inhibitors (MAOIs)
Atypical antidepressants

Which of these agents are now considered first-line treatment for depression?

SSRIs
Atypical antidepressants

TRICYCLICS

Give some examples of tricyclic antidepressants.

Tertiary Amine Tricyclics
Amitriptyline—prototype
Imipramine—prototype
Doxepin
Clomipramine
Trimipramine

Secondary Amine Tricyclics
Amoxapine
Maprotiline
Protriptyline
Desipramine
Nortriptyline

What are the physiologic differences between tertiary amine and secondary amine tricyclics?

The secondary amine tricyclics in general are less likely to cause sedation, hypotension, and anticholinergic effects. However, they are more likely to induce psychosis.

What is the mechanism of action of all the tricyclics?

These drugs are thought to increase levels of norepinephrine and serotonin in the synaptic cleft by blocking neuronal reuptake. They also block histamine, cholinergic, and α -adrenergic receptors, which accounts for a large proportion of their side effects. Tricyclics are also thought to cause a down-regulation of monoamine receptors; this may account for some of their therapeutic benefit.

Do these drugs elevate mood in normal individuals?

No. These drugs are not CNS stimulants.

What are the clinical indications for tricyclics?

Mood disorders (depression primarily)
Panic disorder
Generalized anxiety disorder
Posttraumatic stress disorder
Obsessive-compulsive disorder
(clomipramine)
Pain disorders
Enuresis in children (imipramine)

How are tricyclics administered?

They are well absorbed orally, and penetrate into the CNS easily.

How are these drugs metabolized?

They undergo significant first-pass metabolism in the liver; they are conjugated with glucuronic acid and excreted through the kidneys.

Which of the tricyclics are most efficacious?

All are equally efficacious.

When should a physician expect to see a change in the patient's mood?

Although the uptake mechanism is inhibited almost immediately, antidepressant clinical effects may require 2 to 8 weeks to become apparent. This suggests that their mechanism of action is not completely understood.

What are the signs and symptoms of tricyclic toxicity?

Anticholinergic side effects—blurred vision, hot dry skin, constipation, confusion, urinary retention
Autonomic effects—orthostatic hypotension
ECG changes—widening of the QRS complex, arrhythmias
Weight gain
Sedation due to histamine blockade
Possible lowering of seizure thresholds

Can tricyclics and MAOIs be given together for added benefit?

No! There is a chance that this combination can lead to severe convulsions and coma.

SEROTONIN-SPECIFIC REUPTAKE INHIBITORS (SSRIS)

Give some examples of SSRIs.

Fluoxetine (Prozac)—prototype
Sertraline (Zoloft)
Paroxetine (Paxil)
Fluvoxamine (Luvox)

What is their mechanism of action?

Inhibition of serotonin reuptake without significant effects on norepinephrine and dopamine

When would these drugs be indicated?

Depression is the primary reason for prescribing these drugs. Fluoxetine is also used to treat obsessive-compulsive disorder.

How are SSRIs administered?

Orally

How are they metabolized?

By the cytochrome P-450 system.
Fluvoxamine is a potent P-450 inhibitor.

Describe the side-effect profile of SSRIs.

In general SSRIs have fewer side effects (anticholinergic, antihistaminic, α -adrenergic blockade) than do other classes of antidepressants.

What adverse symptoms may a patient taking SSRIs experience?

Nausea
Diarrhea
Nervousness
Insomnia
Dizziness
Impotence
Decreased libido

When are SSRIs contraindicated?

SSRIs are contraindicated in combination therapy with monoamine oxidase inhibitors (MAOIs) because this combination may result in the “serotonin syndrome,” characterized by hyperthermia, muscle rigidity, myoclonus, and rapid changes in mental status.

MONOAMINE OXIDASE INHIBITORS (MAOIs)

What is monoamine oxidase?

MAO is a mitochondrial enzyme that is involved in the metabolism of catecholamine neurotransmitters.

Where are the highest concentrations of this enzyme?

In the liver, GI tract, and CNS

Describe the mechanism of action of the MAOIs.

Two types of MAO exist: MAO-A and MAO-B.

Within the neurons, MAO-A is responsible for the inactivation of any serotonin or norepinephrine that may leak out of presynaptic storage vesicles. When MAO-A is blocked, these neurotransmitters accumulate and are released into the synapse. MAO-B is responsible for the metabolism of dopamine and works in a similar manner. In general, the MAOIs are nonspecific inhibitors of MAO, except for selegiline, which is a specific inhibitor of MAO-B.

What are the MAOIs indicated for?

Treatment of atypical depression (with phobia or psychotic features). Other classes of antidepressants are more frequently used today because they have fewer toxic effects.

Describe the pharmacologic properties of MAOIs.

They are well absorbed orally. They are metabolized by acetylation in the liver (half-life, 2–3 hours). They require 2 to 4 weeks of treatment to reach a steady-state plasma level.

What are the adverse effects of MAOIs?

Hypertensive crisis (headache, hypertension, arrhythmias, and possibly stroke) if the patient does not avoid

eating foods high in tyramine (cheeses, chicken liver, beer, and red wine). At increased levels, tyramine will release catecholamines from storage vesicles and therefore will act as a pressor agent. Hypertensive crisis can also occur when MAOIs are administered with meperidine.

Orthostatic hypotension
Dry mouth, blurred vision
Weight gain

ATYPICAL ANTIDEPRESSANTS

Give two examples of atypical antidepressant agents.

1. Trazodone (Desyrel)
2. Bupropion (Wellbutrin)

Why are these drugs considered atypical?

Their mechanism of action is less well defined than that of the traditional antidepressants.

Trazodone

What is it?

An antidepressant similar in structure to the benzodiazepine alprazolam (Xanax), but more specific for inhibition of serotonin reuptake

When is trazodone indicated?

To treat depression. It is particularly effective for improving sleep.

Where is this drug metabolized?

In the liver (excreted by the kidneys)

Describe the adverse effects.

Sedation
Orthostatic hypotension
Nausea
Headache and dizziness
Agitation
Rare anticholinergic side effects

Bupropion

Describe this drug's mechanism of action.

It is not clearly known.

What are the indications for bupropion?

Depression

What toxicities are associated with bupropion?	Headache Nausea Tachycardia Restlessness
What is the advantage for using bupropion?	There are no side effects related to sexual dysfunction, such as those that occur with SSRIs.

ANTIMANIC AGENTS

What is mania?	Elevated mood with grandiose ideas, expansiveness, pressured speech, flight of ideas, decreased sleep, and increased activity.
In what conditions is mania seen?	Affective disorders such as bipolar disorder
Give some examples of antimanic agents.	Lithium—drug of choice Anticonvulsants (valproic acid and carbamazepine)—See <i>Chapter 14</i> — <i>Anticonvulsants</i> for further discussion of anticonvulsants.

LITHIUM

What is it?	A light alkali metal available in carbonate, slow-release, and controlled-release forms
How does lithium work?	The mechanism is unclear; it is thought to block the enzyme inositol-1-phosphatase, which affects neurotransmitters.
What is lithium's major indication?	It is primarily used in bipolar disorder—both manic and depressive episodes respond.
Describe some other uses.	This drug is also used as an adjuvant with antidepressants to treat major depression, and with antipsychotics to treat schizophrenia.
What are the pharmacokinetic properties of lithium?	It is well absorbed orally and excreted in the urine.
When is lithium contraindicated?	Pregnancy—it is teratogenic.

What adverse effects should physicians watch for when administering lithium?

Acute intoxication—severe tremor, ataxia, seizures, confusion, and coma
 Nephrogenic diabetes insipidus
 Weight gain, vomiting, abdominal cramps, and diarrhea
 Disturbances in thyroid function (Monitor TSH for lithium-induced hypothyroidism.)
 Depression of T-wave on ECG
 Leukocytosis

What substances affect lithium plasma levels?

Excessive intake of sodium lowers lithium levels
 Thiazide diuretics increase plasma levels of the drug.

How is lithium toxicity treated?

Overdoses are cleared by diuretics. As previously mentioned, *do not use thiazides* because they increase plasma levels of the drug. Use sodium bicarbonate, or dialysis if necessary.

14

Anticonvulsants

What is a seizure?

An abnormal, synchronized, electrical depolarization of neurons in the central nervous system

Name five major causes of seizures.

1. Idiopathic
2. CNS infections
3. Fever
4. Metabolic defects
5. Cerebral trauma

List the different types of seizures.

Partial
Generalized tonic-clonic
Status epilepticus
Absence
Febrile
Myoclonic

What is a partial (focal) seizure?

A seizure in which abnormal discharges occur from a focal area within the brain. There are two types of partial seizures: simple and complex.

What are the characteristics of a simple partial seizure?

A simple partial seizure involves a focal neurologic symptom that can be sensory (for example, auditory or visual hallucinations), motor, or psychomotor. Consciousness is always retained.

What happens in a complex partial seizure?

The initial focus of abnormal discharge spreads so that the patient will lose consciousness and have postictal (post-seizure) confusion. Symptoms can include coordinated motor activity and olfactory hallucinations.

Where do complex partial seizures originate?

The majority originate in the temporal lobe.

What part of the brain is involved in a generalized tonic-clonic (grand mal) seizure?

The entire cerebral cortex

Name and describe the typical phases of a grand mal seizure.

Tonic phase—loss of consciousness, rigidity, loss of bowel and bladder control

Clonic phase—jerking movements of the entire body

Can a partial seizure develop into a grand mal seizure?

Yes—this is known as partial seizure with secondary generalization.

What is status epilepticus?

Continuous seizures not separated by any periods of regained consciousness. This condition is a medical emergency.

What are the characteristics of absence (petit mal) seizures?

They usually occur in children 2 to 12 years of age.

They are characterized by a very brief (10 seconds) loss of consciousness. The child will stop whatever he is doing and stare or have some facial twitching.

Following the attack, the child becomes immediately alert and is seldom even aware that it has occurred.

What are the characteristics of febrile seizures?

They occur in children.

They usually last less than 10 minutes.

The child has a fever, but there is no apparent infection or other defined cause for the seizure.

What are the characteristics of myoclonic seizures?

They are sudden, short episodes of either local or generalized muscle contractions

They can occur at any age.

They are associated with a variety of rare hereditary neurodegenerative disorders.

Define epilepsy.

Epilepsy is a group of chronic syndromes characterized by recurrent seizures with periods of consciousness.

What percentage of the population is affected by epilepsy?

About 1%

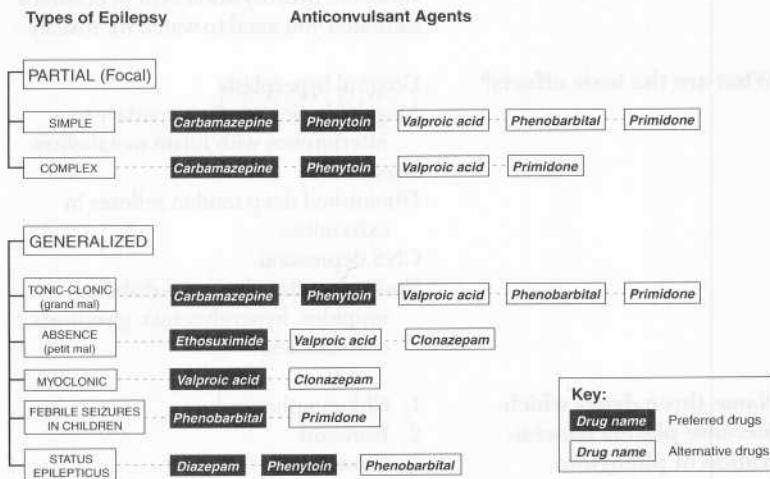


Figure 14-1. Therapeutic indications for anticonvulsant agents. (Adapted and redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 145.)

What are the pharmacologic treatment options for seizures?

Phenytoin
 Carbamazepine
 Phenobarbital
 Primidone
 Valproic acid
 Ethosuximide
 Benzodiazepines
 Gabapentin
 Lamotrigine
 See Figure 14-1.

PHENYTOIN (DILANTIN)

What are the therapeutic uses of phenytoin?

Phenytoin is effective in treating tonic-clonic seizures and partial seizures but not absence seizures. It is also used in the treatment of status epilepticus after the administration of diazepam.

What is the mechanism of action?

Phenytoin binds to and prolongs the inactivated state of Na^+ channels.

Describe the absorption and metabolism of this drug.

Oral absorption is slow. Phenytoin undergoes hydroxylation by the hepatic microsomal enzyme system. At high doses

when the hydroxylation system becomes saturated you need to watch for toxicity.

What are the toxic effects?

Gingival hyperplasia
Megaloblastic anemia secondary to interference with folate metabolism
Hirsutism
Diminished deep tendon reflexes in extremities
CNS depression
Endocrine disturbances—diabetes insipidus, hyperglycemia, glycosuria, osteomalacia

Name three drugs which increase plasma concentration of phenytoin.

1. Chloramphenicol
2. Isoniazid
3. Cimetidine

Name one drug which is well known to decrease plasma concentrations of phenytoin.

Carbamazepine

Is phenytoin teratogenic?

Yes. It produces fetal hydantoin syndrome, which is characterized by prenatal growth deficiency and mental deficiencies. There is also an increased incidence of congenital malformations such as cleft palate and heart malformations.

CARBAMAZEPINE (TEGRETOL)

What is the therapeutic use of carbamazepine?

It is the drug of choice for treating partial and tonic-clonic seizures. It is also the drug of choice for treating trigeminal neuralgia.

What is its mechanism of action?

It prolongs the inactivated state of Na^+ channels.

What are the absorption and metabolism of this drug?

Carbamazepine is absorbed slowly when given orally and is metabolized by the P-450 system.

Which drugs inhibit the metabolism of carbamazepine?

Erythromycin
Isoniazid
Propoxyphene

Verapamil
Cimetidine

What are carbamazepine's adverse effects?

Acute intoxication can lead to respiratory depression, stupor, or coma.
Severe liver toxicity—Patients need frequent liver function tests while receiving this drug.
Aplastic anemia
Agranulocytosis
Patients frequently complain of drowsiness, ataxia, nystagmus, and vomiting.

PHENOBARBITAL (LUMINAL)

What is the classification of this drug?

It is a barbiturate.

State its mechanism of action.

Potentiation of synaptic inhibition through an action on the GABA receptor

What are phenobarbital's therapeutic uses?

1. It is the drug of choice for treating febrile seizures; it is also used to treat grand mal seizures in children.
2. It is good for treating partial seizures and tonic-clonic seizures; however, its sedative effects have reduced its use as a primary agent.

What are the absorption and metabolism of phenobarbital?

The drug is well absorbed orally; 75% of it is metabolized in the liver. It is a potent inducer of the cytochrome P-450 system. The metabolic by-products are excreted in the urine.

State phenobarbital's adverse effects.

Sedation
Nystagmus
Psychotic reactions
Hypersensitivity reactions—Stevens-Johnson syndrome

PRIMIDONE (MYSOLINE)

What drug is primidone structurally related to?

It is related to phenobarbital and it works the same way as phenobarbital.

When is this drug used?

Primidone is an alternative choice for adults who have partial seizures (both simple and complex) and generalized tonic-clonic seizures.

How is this drug metabolized?

Primidone is converted to phenylethylmalonamide (PEMA) and to phenobarbital in the liver.

What are its adverse effects?

This drug's toxic effects are very similar to those of phenobarbital:

Sedation
Ataxia
Nausea
Vomiting
Drowsiness

VALPROIC ACID (DEPAKENE)

What are the indications for use of this drug?

Valproic acid is the most effective agent for treating myoclonic seizures. It is also used in the treatment of absence seizures.

How does this drug work?

It prolongs the inactivated state of Na^+ channels. It may also increase GABA concentrations in the brain.

What is the route of administration?

Valproic acid is well absorbed orally. Once absorbed, approximately 90% of the drug is bound to plasma proteins.

How is it metabolized?

The drug is extensively metabolized in the liver by the cytochrome P-450 system. However, it does not induce the enzymes of this system. Approximately 3% of the drug is excreted unchanged.

What side effects should you watch for when administering valproic acid?

Hepatotoxicity—This drug may cause a fulminant hepatitis, which can be fatal.
Nausea and vomiting
Sedation
Tremor

Should pregnant mothers be given valproic acid?

No! The incidence of neural tube defects is very high if this drug is taken during the first trimester of pregnancy.

ETHOSUXIMIDE (ZARONTIN)

What is this drug used for?	Ethosuximide is the drug of choice for treating absence seizures.
What is its mechanism of action?	Ethosuximide inhibits Ca^{2+} influx through T-type channels in the thalamic neurons.
What are the absorption and metabolism of this drug?	It is well absorbed orally. The majority of the drug is metabolized by the cytochrome P-450 system in the liver. It does not induce P-450 enzyme synthesis.
State the toxic effects.	<p>Dizziness</p> <p>Agitation</p> <p>GI distress</p> <p>Confusion</p> <p>Blood dyscrasias such as leukopenia, aplastic anemia, and thrombocytopenia may occur in extremely sensitive patients.</p> <p>Skin reactions such as Stevens-Johnson syndrome have been reported.</p>

BENZODIAZEPINES

See *Chapter 11—Anxiolytics, Hypnotics, and Sedatives* for further details about benzodiazepines.

Give three examples of benzodiazepines that are used for anti-epileptic purposes.	<ol style="list-style-type: none"> 1. Diazepam (Valium) 2. Clonazepam (Klonopin) 3. Clorazepate (Tranxene)
What is the therapeutic use of these drugs?	<p>Intravenous diazepam is the drug of choice for initiating treatment of status epilepticus.</p> <p>Clonazepam can be used for treating myoclonic seizures in children.</p> <p>Clorazepate may be used for partial seizures in combination with other drugs.</p>
State the adverse effects of benzodiazepines.	The benzodiazepines have relatively minor side effects, but you should watch for the following:

Drowsiness
Respiratory depression
Cardiac depression

GABAPENTIN (NEURONTIN)

State the therapeutic use of this drug.	Gabapentin is used to treat partial seizures with and without secondary generalization. This drug is used in adults in combination with other antiseizure drugs.
What is the mechanism of action?	Gabapentin has been found to promote release of GABA.
What is the metabolism of this drug?	It is excreted unchanged in the urine.
State the toxic effects.	Ataxia Somnolence Fatigue

LAMOTRIGINE (LAMICTAL)

What is the therapeutic use of lamotrigine?	It is used to treat partial seizures in adults in combination with other drugs.
What is its mechanism of action?	Lamotrigine blocks sustained repetitive firing by blocking voltage-dependent Na^+ channels.
Name the site of metabolism.	This drug is metabolized in the liver.
What are the toxic effects of lamotrigine?	Dizziness Blurred vision Rash

15

Drugs Used to Treat Parkinson's Disease and Other Movement Disorders

PARKINSON'S DISEASE

What is Parkinson's disease?

A movement disorder that has the following four cardinal characteristics:

1. Resting tremors
2. Muscle rigidity
3. Bradykinesia
4. Abnormal gait and posture

What is the pathophysiology of this disease?

The disorder is thought to occur because of a loss of dopamine in the nigrostriatal pathway (Figure 15-1). The loss of dopamine disrupts the delicate balance between the cholinergic and dopaminergic systems within the striatum and basal ganglia.

What are the pharmacologic treatment options?

Levodopa
Carbidopa
Bromocriptine
Pergolide
Amantadine
Selegiline
Antimuscarinic agents

Can these drugs cure?

No! Pharmacologic treatments can only offer temporary relief; they neither reverse nor arrest the disease process.

What is the treatment strategy?

The ultimate goal is to reestablish the balance between dopamine and acetylcholine in the brain. This can be

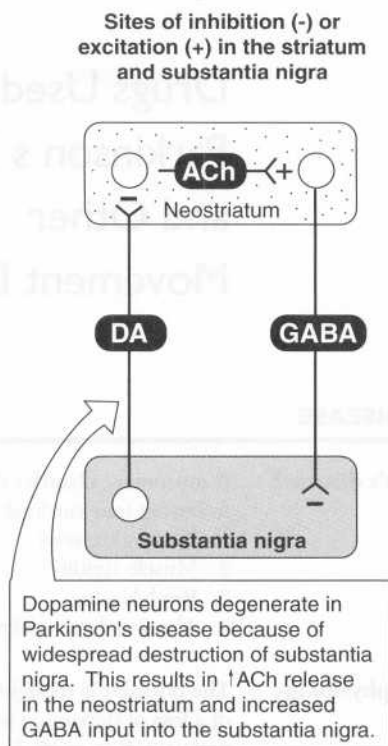


Figure 15-1. Effects of dopaminergic neuron loss in Parkinson's disease. DA = dopamine; GABA = γ -aminobutyric acid; ACh = acetylcholine. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 84.)

accomplished by either (1) increasing dopamine in the nigrostriatal system, or (2) reducing the cholinergic output of the striatum.

LEVODOPA (Larodopa)

What is it?

This metabolic precursor of dopamine is a first-line drug in the therapy for Parkinson's disease.

What is the advantage of using a precursor to dopamine?

Dopamine itself does not cross the blood-brain barrier. However, levodopa is transported into the brain and subsequently converted to dopamine in the basal ganglia.

What are the disadvantages of using this drug alone?

Large doses of levodopa are required if it is used alone because this drug is decarboxylated in the periphery to dopamine. Levodopa is typically used in combination with another drug such as carbidopa.

What are the pharmacokinetics of levodopa?

This drug is absorbed well from the GI tract. However, if ingested with high-protein meals, the transport of levodopa across the blood-brain barrier is impaired because of competition from neutral amino acids.

What is the on-off phenomenon?

Because levodopa has an extremely short half-life, plasma levels may drop suddenly. This may cause sudden immobility, tremors, and cramps. The development of rapid changes in clinical response to the drug is known as the on-off phenomenon.

What drugs should NOT be given with levodopa?

Nonselective monoamine oxidase inhibitors—This combination will

result in excess dopamine in the periphery, which could lead to a life-threatening hypertensive crisis.

Pyridoxine—This drug diminishes the effectiveness of levodopa because it increases peripheral breakdown of the drug.

Antipsychotics—these drugs block dopamine receptors

What are the adverse effects of levodopa?

Nausea, vomiting, arrhythmias, and postural hypotension—due to levodopa being converted to dopamine in the periphery

Dyskinesia, hallucinations, restlessness, and confusion—due to overstimulation of central dopamine receptors

CARBIDOPA (Lodosyn)

What is it?

A dopamine decarboxylase inhibitor that does not cross the blood-brain barrier

Why use it?

When administered with levodopa, carbidopa reduces the metabolism of dopamine in the periphery and therefore

increases the availability of dopamine to the CNS. The addition of carbidopa reduces by fourfold the amount of levodopa needed.

What is the efficacy of levodopa/carbidopa (Sinemet) treatment?

Two thirds of persons who follow this regimen show some remission of symptoms (especially bradykinesia) in the first 2 years of treatment. Treatment efficacy declines as the disease progresses. This occurs because levodopa requires some healthy dopaminergic neurons to be effective.

BROMOCRIPTINE (Parlodel)

What is it?

Bromocriptine is an ergotamine derivative that acts as a dopamine receptor agonist at D_2 receptors. It is a second-line drug after levodopa.

What are its therapeutic uses?

Bromocriptine is used in conjunction with levodopa. It may allow reduction in the levodopa maintenance dosage and therefore may reduce the occurrence of side effects associated with long-term levodopa use. Bromocriptine has very little effect on parkinsonian symptoms when used alone; however, when used in conjunction with levodopa, it helps relieve akinesia, rigidity, and tremor. In addition to being used to treat Parkinson's disease, it is the drug of choice to treat cases of hyperprolactinemia (👉 common board question).

What are the adverse effects of this drug?

Hallucination, delirium, nausea, and vomiting
Cardiac arrhythmia, postural hypotension
Erythromelalgia

PERGOLIDE (Permax)

How does pergolide work?

It works in a manner similar to bromocriptine; however, it is a dopamine agonist at both D_1 and D_2 receptors.

What role does it have in the treatment of Parkinson's disease? It is usually used in combination with levodopa

What are the adverse effects? Confusion
Hallucinations
Orthostatic hypotension
Urinary tract infections

SELEGILINE (Eldepryl)

What is its mechanism of action? Selegiline selectively inhibits monoamine oxidase B (MAO-B), which metabolizes dopamine. Monoamine oxidase A (MAO-A), however, is not affected unless extremely high doses of selegiline are given.

What is its therapeutic use? Because it decreases the metabolism of dopamine in the periphery, selegiline increases dopamine levels in the brain. The effects of levodopa are enhanced when used in conjunction with selegiline; however, there is a threat of hypertensive crisis when this drug is administered in high dosages.

AMANTADINE (Symmetrel)

What is this drug's classification? Amantadine is an antiviral agent used to treat influenza.

What is its mechanism of action? The exact mechanism is unknown. Amantadine appears to either enhance the release of dopamine from surviving nigral neurons or inhibit the reuptake of dopamine at synapses.

What is its therapeutic use? Amantadine may improve bradykinesia, tremor, and rigidity when used along with levodopa. It is usually effective for only a few weeks but seems to be more effective than anticholinergic agents.

What are the toxic effects of this drug? Restlessness, agitation, confusion
Orthostatic hypotension
Peripheral edema
Livedo reticularis (skin rash)

ANTICHOLINERGIC AGENTS

Name three examples of this class of drugs.

The three most commonly used anticholinergics are:

1. Benztropine (Cogentin)
2. Biperiden (Akineton)
3. Trihexyphenidyl (Artane)

Why use them?

These drugs help reduce the cholinergic output of the striatum (see Figure 15-1). Again, this is another method to restore balance between dopamine and acetylcholine within the nigrostriatal system.

What is their therapeutic efficacy?

These drugs are much less efficacious than levodopa. They are commonly used adjuvantly in parkinsonian therapy. They primarily help reduce tremor, rigidity, and akinesia; secondary symptoms such as drooling are also reduced.

What are their adverse effects?

The following are caused by decreased parasympathetic response:

Sedation
Urinary retention
Dry mouth
Constipation
Mental confusion

ADDITIONAL MOVEMENT DISORDERS

What is drug-induced parkinsonism?

Parkinsonian symptoms can be caused by potent antipsychotic agents such as haloperidol because they block dopamine receptors.

What is the treatment for drug-induced parkinsonism?

There are three treatment options:

1. Lower the drug levels.
2. Change the drug to a less potent one.
3. Use an anticholinergic agent.

Define Huntington's disease.

A genetic disorder due to a single defect on chromosome 4

What are the symptoms?

Individuals who have this disease display dementia and/or chorea.

- What is the pathophysiology?** This disease is thought to occur because of excessive dopaminergic activity and diminished γ -aminobutyric acid (GABA) functions in the basal ganglia (caudate and putamen).
- What is the treatment?** Dopamine blockers such as haloperidol (Haldol) or tetrabenazine are used to treat this disorder.
- What is Tourette's syndrome?** A disease characterized by abnormal tics and facial movements
- What is the treatment?** Clonidine (Catapres). Haloperidol has also been used.
- Define Wilson's disease.** Wilson's disease is a genetic disorder of copper metabolism. Excess copper is deposited in the liver, brain, and other tissues.
- What is the treatment for Wilson's disease?** A copper chelating agent known as penicillamine (Depen)

16

Anesthetics

What are the two major classes of anesthetic agents?

General and local

Describe the routes of administration and primary actions of each of these two classes.

General anesthetics are given either as **inhaled** or **intravenous** agents; they primarily have CNS effects. Local agents are injected at the operative site to block nerve conduction.

GENERAL ANESTHETICS

What are the stages of general anesthesia?

There are four stages:

Stage I—Analgesia—Reduced sensation of pain; the patient remains conscious and conversational.

Stage II—Excitement—Delirium and combative behavior ensue; there is an increase in blood pressure and respiratory rate.

Stage III—Surgical anesthesia—The patient is unconscious, and regular respiration returns; there is muscle relaxation and decreased vasomotor response to painful stimuli.

Stage IV—Medullary paralysis—Respiratory drive decreases and vasomotor output diminishes; death may quickly ensue.

How do the pharmacokinetics of anesthetics affect these stages?

With slow-onset agents (for example, ether), all four stages are discernible. Faster-acting agents allow for quicker progression through the stages.

What is induction of anesthesia?

The time from administration of a general anesthetic to the achievement of surgical anesthesia

What is induction dependent upon?

How fast the anesthetic reaches the CNS

How are the complications of anesthetic induction avoided?

An ultra-fast-acting, short-lived agent (such as propofol) is given IV so that the patient will rapidly progress through the first and second stages of anesthesia.

What is recovery?

Simply, the reverse of induction

What does recovery depend upon?

How quickly the anesthetic is removed from the CNS

For inhaled anesthetics, what five factors influence the rate of induction?

1. Solubility
2. Pulmonary ventilation
3. Partial pressure of the inhaled agent
4. Alveolar blood flow
5. Arteriovenous concentration gradient

Describe how solubility affects the rate of induction.

The blood-gas partition coefficient is an index of solubility; a low coefficient implies relative insolubility. An agent with a low solubility requires fewer molecules to raise the partial pressure of the agent in the blood; thus, the equilibrium between alveolar partial pressure and arterial partial pressure is achieved rapidly, which leads to faster induction. Recovery is likewise hastened when the anesthetic agent is discontinued.

How does pulmonary ventilation affect the rate of induction?

The rate and depth of ventilation (the minute ventilation) affects the rate of increase in partial pressure of the anesthetic in the blood. An increase in the minute ventilation results in an increased amount of agent. This effect is most important for agents with low solubility because they require greater amounts of agent to achieve equilibrium.

Describe how partial pressure of the inhaled agent affects the rate of induction.

An increased concentration in the inhaled air mixture leads to greater concentration at the alveoli and thus increases the arterial partial pressure of the agent. In clinical practice, a greater concentration is given initially to speed induction, and then it is reduced to a maintenance level.

How does alveolar blood flow affect the rate of induction?

Increased flow allows for more rapid uptake of the agent and quicker effect on the CNS.

Describe how the arterio-venous concentration gradient affects the rate of induction.

This is dependent on the uptake of the agent by tissue. A high rate and extent of tissue uptake will decrease the venous concentration of the anesthetic. As a result, it will take a longer time for the anesthetic concentration of arterial and venous blood to equilibrate.

What factors influence tissue uptake of an anesthetic?

Anesthetic uptake is influenced by many of the same factors that influence transfer from lung to blood: tissue-blood partition coefficients, rates of blood flow to the tissues, and concentration gradients are all important factors. Highly perfused tissues (brain, heart, liver, kidneys, and splanchnic bed) will exert the greatest influence on arteriovenous concentration. Skin and muscle undergo slow diffusion because these tissues are less richly perfused and thus exert less of an effect on arteriovenous concentration.

What is the molecular mechanism of action for general anesthetics?

The mechanism is not clear. All anesthetics have the common property of increasing the threshold of action potentials and inhibiting the rapid increase in membrane permeability to sodium ions. The effect of these changes is not known. No receptors have been found to interact with general anesthetics.

INHALED AGENTS

Name six inhaled agents.

1. Halothane
2. Enflurane
3. Isoflurane
4. Desflurane
5. Sevoflurane
6. Nitrous oxide

How is the potency of inhaled anesthetics defined and measured?

Using the concept of **MAC**

What is MAC? MAC is the *minimum alveolar concentration* of an anesthetic necessary to eliminate movement among 50% of patients challenged by a standardized skin incision.

How does MAC relate to potency? The greater the MAC of an agent, the greater the concentration needed to provide anesthesia. Thus, an agent with a high MAC has a low potency (for example, nitrous oxide).

How can the MAC of any inhaled agent be reduced? By using the agent in conjunction with analgesics such as opioids or sedative hypnotics

Halothane

Describe this drug. The first of the halogenated volatile anesthetics to be developed, halothane has been largely replaced by more modern agents.

What is its clinical indication? It is still used in the pediatric population because of its pleasant odor and lack of hepatotoxicity.

Is this drug metabolized? Approximately 20% is eliminated by metabolism; the remainder is eliminated unchanged in expired air.

What is halothane's MAC? 0.75%

What are the cardiovascular effects of halothane? Halothane sensitizes the myocardium to the effects of catecholamines (thus increasing the risk of arrhythmia), decreases heart rate and cardiac output, and leads to lowered BP and peripheral resistance.

Are there any toxic effects? Hepatotoxicity—**Halothane hepatitis**, a fulminant hepatic necrosis—has been associated with halothane, although halothane has not been directly implicated as the cause.
Malignant hyperthermia—Halothane can induce malignant hyperthermia secondary to its absorption and metabolism in skeletal muscle.

What is malignant hyperthermia? A potentially fatal reaction to any of the inhaled anesthetics, which results in hyperthermia, metabolic acidosis, tachycardia, and accelerated muscle contraction

How is this condition treated? With dantrolene and cessation of the offending agent

Enflurane

What are its clinical indications? Rapid induction of general anesthesia

Is this drug metabolized? Approximately 2% of the agent is metabolized to a fluoride ion, which is then excreted by the kidney. The rest is eliminated unchanged in the expired air.

What is enflurane's MAC? 1.6%

What are this drug's cardiovascular effects? Enflurane is similar to halothane in that it decreases heart rate, BP, and peripheral resistance. Although it has less of a sensitizing effect on the myocardium than does halothane, enflurane can nevertheless produce cardiac arrhythmia.

Describe the toxic effects. The fluoride ion resulting from enflurane's metabolism can be nephrotoxic. A decrease in the kidney's concentrating ability after prolonged exposure to enflurane has been observed in patients with preoperative kidney insufficiency.

Isoflurane

What are the clinical indications? General anesthesia

Is this drug metabolized? Isoflurane is minimally metabolized; almost all of the drug is eliminated unchanged in the expired air.

What is its MAC? 1.4%

What are the cardiovascular effects? Increases heart rate
Does not effect cardiac output

	Can lower BP and reduce peripheral vascular resistance profoundly
	Does not sensitize the myocardium to catecholamines
	Does not induce arrhythmia
Are there any toxic effects?	Potential for malignant hyperthermia

Desflurane

Describe this drug's clinical indications.	General anesthesia
Does this drug undergo metabolism?	Desflurane is eliminated unchanged in the expired air.
What is its MAC?	6%
What are desflurane's cardiovascular effects?	Its profile very similar to that of isoflurane.
Are there toxic effects?	Potential for malignant hyperthermia

Sevoflurane

What are the clinical indications?	General anesthesia
Does sevoflurane undergo metabolism?	A small percentage of this agent is metabolized to fluoride ion; the remainder is eliminated unchanged in the expired air.
What is this drug's MAC?	2%
Describe sevoflurane's cardiovascular effects.	It has a cardiac profile similar to that of both desflurane and isoflurane.
Are there any toxic effects?	Although metabolism of sevoflurane produces a fluoride ion, it does not affect renal function like enflurane does. It has been hypothesized that because sevoflurane is not metabolized in the kidney (as enflurane is), toxic effects do not occur.

Nitrous Oxide ("Laughing Gas")

What are the clinical indications?	Induction of general anesthesia
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How is this drug administered? Because of its low potency, nitrous oxide must be used in conjunction with other anesthetics (either inhaled or intravenous) for effective general anesthesia.

Is nitrous oxide metabolized? No

What is its MAC? 100%—Even if 100% nitrous oxide were given to patients, surgical anesthesia would not be achieved (and profound hypoxia would result!).

Are there cardiovascular effects? Nitrous oxide minimally affects the cardiovascular system.

Name a major contraindication to the use of nitrous oxide. If nitrous oxide is administered to patients who have closed air cavities (e.g., pneumothorax), the gas will diffuse into the cavity and increase the pressure within it.

What special considerations should be taken into account during the recovery phase? Care must be taken to adequately oxygenate the patient, because nitrous oxide will diffuse from the blood into the alveoli so quickly that it entirely replaces oxygen, which results in a **diffusion hypoxia**.

What are the toxic effects? Nitrous oxide can cause bone marrow depression with prolonged administration; high concentrations may cause neuropathies.

INTRAVENOUS AGENTS

What are the classes of intravenous anesthetics? Barbiturates, benzodiazepines, opioids, and dissociative agents

Ultra-Short-Acting Barbiturates

Thiopental

What is the clinical indication for this drug? Thiopental is used for the induction of anesthesia in combination with inhaled anesthetics. It has a rapid onset of action, with unconsciousness occurring 15 to 30 seconds after administration.

What is this drug's mechanism of action?

Thiopental binds to the **γ -aminobutyric acid A (GABA_A)** receptor, which results in prolonged opening of the chloride channel. The neuron's membrane is thus hyperpolarized, which creates a reduction of neuronal excitability.

What phenomenon is responsible for this drug's fast onset of action and short duration?

Thiopental has **high lipid solubility** and thus crosses the blood-brain barrier very quickly. However, the drug just as quickly diffuses out of the brain and other highly vascularized organs, and is rapidly redistributed to muscle, fat, and other body tissues, which accounts for its short duration.

Is thiopental metabolized?

Yes. Metabolism (in the liver) occurs much more slowly than does redistribution. Nearly 99% of the drug is metabolized; thus, after large doses (especially continuous infusions), recovery can be very slow.

What are the cardiovascular effects?

Thiopental reduces blood pressure and cardiac output, but it does not affect peripheral resistance.

Describe the respiratory effects.

Thiopental depresses the respiratory center of the brain and blunts the response to CO₂ and hypoxia. This effect on cerebral blood flow makes thiopental a desirable agent in patients who have cerebral edema.

What are this drug's effects on cerebral blood flow?

It decreases cerebral blood flow and oxygen consumption by the brain.

Are there any side effects?

Thiopental may induce laryngospasm and bronchospasm. It may also exacerbate acute intermittent porphyria by inducing the synthesis of hepatic δ -aminolevulinic acid synthase (thiopental has precipitated porphyric crisis).

Benzodiazepines—Midazolam, Diazepam, Lorazepam

See Chapter 11—Anxiolytics, Hypnotics, and Sedatives for further information on the benzodiazepines.

Describe the clinical indication for these drugs.

Benzodiazepines are used for preoperative sedation, intraoperative sedation for procedures not requiring analgesia (colonoscopy, cardioversion, and so forth), and as part of **balanced anesthesia** (using several agents simultaneously to obtain surgical anesthesia).

What is the mechanism of action?

Benzodiazepines bind GABA receptors, which results in reduced neuronal excitability. These drugs have a much slower onset of action than do the barbiturates.

Why is midazolam used as a pre-anesthetic medication?

This drug produces antegrade amnesia (loss of memory of events after administration of the drug), which calms the patient.

Why is midazolam also the preferred benzodiazepine for induction and maintenance of anesthesia?

Midazolam has a shorter onset of action, greater potency, and more rapid elimination when compared to other benzodiazepines.

What are the side effects of benzodiazepines?

Alone, these drugs can cause moderate circulatory and respiratory depression. If used with opioids, cardiovascular collapse and respiratory arrest can occur.

Are there other uses for these drugs?

They are used to control seizures and in the alcohol withdrawal process to control symptoms.

Is there a benzodiazepine antagonist?

Flumazenil antagonizes the CNS depression caused by benzodiazepines.

Opioids—Fentanyl, Morphine

What are the clinical indications for these drugs?

Opioids are used as general anesthetics in patients undergoing cardiac surgery or other major surgeries for which cardiac reserve is limited.

Why is fentanyl used more often than morphine?

It has a greater potency and less impact on respiratory drive than does morphine.

Are there any side effects?	IV opioids can cause chest wall rigidity, which makes ventilation more difficult. Postoperative respiratory depression can occur. Intraoperative awareness with unpleasant postoperative recall may occur.
Is there an opioid antagonist?	Naloxone reverses the respiratory and CNS effects of opioids.
What is Innovar?	Innovar is a combination of fentanyl and droperidol. When used with nitrous oxide, Innovar produces neurolept-anesthesia (combined analgesia and amnesia).

Other Agents

Propofol (Diprivan)

Describe this drug's clinical indications.	Induction of anesthesia
What are the pharmacologic characteristics of this drug?	Ultrafast-acting drug with pharmacodynamics similar to that of thiopental High lipid solubility Very quick distribution to highly vascularized sites (e.g., the brain) Rapid diffusion back into the blood, with subsequent redistribution
Why is propofol preferred over thiopental for induction of anesthesia?	Rate of onset very similar to thiopental Recovery is quicker, with patients able to ambulate sooner than with other IV anesthetics Patients report less nausea and emesis No cumulative effect from propofol administration or delayed recovery after prolonged infusion
How is propofol metabolized?	It is rapidly metabolized by liver and other extrahepatic enzymes (10 times more quickly than is thiopental).
What are the side effects?	Hypotension Negative inotropic effects Pain at the site of injection (most commonly encountered side effect) Apnea

Does propofol have any other uses?

Propofol is often used in the critical care setting as a continuous infusion to provide prolonged sedation.

Ketamine

Describe the clinical indications.

Ketamine, because of its unique cardiovascular effects, is used in trauma cases where cardiovascular support is necessary. It is also used in children undergoing painful procedures (dressing changes of burns) or to facilitate cooperation during radiographic procedures.

What is the mechanism of action?

Ketamine produces a **dissociative anesthesia** characterized by catatonia, amnesia, and analgesia without actual loss of consciousness.

What are the cardiovascular effects?

Ketamine is unique in that it produces cardiovascular stimulation, with heart rate, arterial blood pressure, and cardiac output all usually significantly increased. This drug stimulates the sympathetic nervous system, which causes the release of catecholamines.

Is ketamine used in head trauma cases?

No, because it increases cerebral blood flow, oxygen consumption, and intracranial pressure.

What are the side effects?

Ketamine can cause an emergence phenomenon consisting of disorientation, sensory and perceptual illusions, and vivid, often unpleasant dreams.

What can be done to reduce the incidence of this phenomenon?

Use of diazepam 5 to 10 minutes before ketamine administration

Are there other routes of administration?

Yes. Ketamine can be given intramuscularly as well as intravenously.

LOCAL ANESTHETICS

What are the two types of local anesthetics?

The two classes are determined by the bond linking the lipophilic portion of the

molecule with the hydrophilic component—either an **ester** or **amide** bond.

Name the ester anesthetics.

Cocaine
Benzocaine
Procaine
Tetracaine

Name the amide anesthetics.

Lidocaine
Mepivacaine
Bupivacaine
Prilocaine

How does the metabolism of the ester and amide anesthetics differ?

Esters are more rapidly metabolized by blood and tissue esterases, which gives them shorter half-lives. Amides are metabolized by hepatic microsomal enzymes, which results in a longer half-life.

What is the mechanism of action of local anesthetics?

These agents block nerve conduction by inhibiting the voltage-gated sodium channels of the neuronal membrane.

Which nerve fibers are most sensitive to local anesthetics?

Small, unmyelinated fibers that conduct pain, temperature, and autonomic activity are affected first. With increasing concentrations of anesthetic, pain fibers (C and A fibers) are first affected; then sensory fibers (A fibers); and last, motor neurons (A fibers).

What are the clinical indications?

Local anesthetics are used for surface anesthesia, nerve blocks, and spinal and epidural anesthesia. Lidocaine is also a potent anti-arrhythmic.

How is the duration of action of local anesthetics increased?

Adding epinephrine to local anesthetics reduces blood flow to the anesthetized area, thus decreasing the absorption of the drugs and enhancing their duration of action.

Are there any side effects?

Systemic effects of local anesthetics occur with high doses of the drug: CNS disturbances—Lightheadedness,

sensory disturbances, convulsions, coma, and even death at high doses

Cardiovascular effects—Myocardial depression and hypotension, except for cocaine, which causes vasoconstriction and hypertension

17

CNS Stimulants

What is the definition of a CNS stimulant?

A CNS stimulant is a drug that increases motor activity, causes excitement, and decreases feelings of fatigue. CNS stimulants include the methylxanthines, nicotine, and the amphetamines.

METHYLXANTHINES

What are methylxanthines?

A group of psychomotor stimulants including:
Caffeine
Theophylline
Theobromine (found in cocoa but of little interest)

How do methylxanthines work?

Research indicates that methylxanthines increase cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) by **inhibiting phosphodiesterase** and **blocking adenosine receptors**.

CAFFEINE

What are the physiologic effects of caffeine?

Caffeine effects a number of organ systems within the body:

CNS—Caffeine increases motor activity and alertness.

Cardiovascular—Caffeine increases heart rate and contractility.

Smooth muscle—Caffeine and its derivatives relax the smooth muscles of the bronchioles.

Genitourinary—Caffeine can act as weak diuretic and increase urinary output of Na^+ , Cl^- , and K^+ .

Gastrointestinal—Caffeine stimulates

secretion from the gastric mucosa. Therefore, patients who have peptic ulcer disease should be counseled to avoid caffeine.

What are the adverse effects of chronic caffeine use?

At low doses—Insomnia and agitation can occur.

At higher doses (8–10 g)—Emesis, convulsions, and even cardiac arrhythmias can occur.

Do methylxanthines cross the placenta?

Yes, and they are secreted into the mother's milk. Patients should be advised to avoid them during pregnancy and while nursing.

THEOPHYLLINE

See Chapter 28—*Drugs Used to Treat Asthma, Coughs, and Colds*, for additional discussion of theophylline.

What is the therapeutic role of theophylline?

Theophylline can be used in the treatment of asthma, but currently it is not being used frequently because it has a very narrow therapeutic index and is not as effective as the new β agonists.

NICOTINE

How are the physiological effects of nicotine related to the dose?

In low doses, nicotine causes ganglionic stimulation by depolarization. At high doses it causes ganglionic blockade.

What are the physiologic actions of nicotine on the central nervous system?

At low doses—arousal, relaxation, and improved attention

At high doses—central respiratory paralysis caused by disruption of medullary function

How does nicotine affect the peripheral nervous system?

At low doses—increase in blood pressure and heart rate; constriction of blood vessels to the digits and impairment of flow

At high doses—decrease in blood pressure and in action of GI and GU tract due to ganglionic blockade

What are nicotine's therapeutic uses?

Nicotine has no therapeutic uses.

What is nicotine's route of administration?	Absorption occurs through oral mucosa, by inhalation, and transdermally.
What are its adverse effects?	CNS—irritability and tremors Peripheral—intestinal cramps, diarrhea, and increased heart rate and blood pressure
What withdrawal symptoms do nicotine addicts experience?	A craving for tobacco is accompanied by irritability, restlessness, anxiety, and gastrointestinal pain.

AMPHETAMINES

Name three examples of this drug class.	1. Methylphenidate (Ritalin) 2. Methamphetamine (Methedrine)—“speed” 3. Dextroamphetamine (Dexedrine)
How do these drugs work?	Amphetamines work by releasing neuronal stores of catecholamines, especially norepinephrine and dopamine.
What are the physiologic actions of these drugs?	Euphoria Decrease in fatigue Increase in blood pressure Increase in rate of respiration Decrease in appetite
What is their clinical use?	Attention deficit hyperactivity disorder (ADHD)—Methylphenidate is used to alleviate this problem. Appetite control—Amphetamines decrease appetite by blocking the receptors in the lateral hypothalamus. Narcolepsy
What is the route of administration?	Oral
Where are amphetamines metabolized?	In the liver
Does physiologic and psychological dependence occur with amphetamine use?	Yes—amphetamines can be very addictive.
What are the adverse effects of these drugs?	Amphetamines, like caffeine and nicotine, affect multiple organ systems:

Central nervous—insomnia, irritability, convulsions; chronic use can lead to a psychotic state resembling schizophrenia

Gastrointestinal—anorexia, nausea, dry mouth

Cardiovascular—palpitations, angina, arrhythmias, hypertension

Amphetamines are contraindicated with what group of drugs?

The monoamine oxidase (MAO) inhibitors

How is amphetamine overdose managed?

Chlorpromazine is beneficial in amphetamine overdose because it blocks the α receptors which are responsible for the CNS disturbances and hypertension.

Alcohol and Other Drugs of Abuse

ALCOHOL

Name three types of alcohol.

1. Ethanol
2. Methanol
3. Ethylene glycol

This chapter focuses mostly on ethanol use.

What is ethanol's mechanism of action?

Ethanol is a CNS depressant that works through γ -aminobutyric (GABA) receptors to enhance GABA-mediated synaptic transmission.

What is ethanol metabolized to?

Acetaldehyde

Which enzymes are responsible for the first steps in the metabolism of ethanol?

1. **Alcohol dehydrogenase**—a nicotinamide adenine dinucleotide (NAD)-dependent enzyme that metabolizes alcohol at a fixed rate of approximately 7 to 10 g/hr. This enzyme must follow zero-order kinetics because of a limited supply of the NAD cofactor. The enzyme is found primarily in the liver and GI tract.
2. **Microsomal ethanol oxidizing system (MEOS)**—Found mainly in the liver, this enzyme increases in activity with chronic ethanol exposure. This increase may account for the tolerance that develops with regular ethanol use.

What is acetaldehyde further metabolized into?

Acetaldehyde is converted into acetic acid by aldehyde dehydrogenase.

Are there therapeutic indications for ethanol use?

Yes:

1. Methanol overdose

2. Ethylene glycol overdose—Ethanol is used in this circumstance because it preferentially binds to alcohol dehydrogenase, and therefore prevents the formation of toxic metabolites from either methanol or ethylene glycol (Figure 18–1).
3. Recent research indicates that one alcoholic drink (red wine) a day may reduce the risk of coronary artery disease.

What are the *acute* affects of ethanol intoxication?

Euphoria
 Disinhibition
 Slurred speech
 Reduced visual acuity
 Ataxia
 Relaxation of vascular and uterine smooth muscle
 Blood levels of alcohol greater than 300 mg/dL can lead to loss of consciousness and decreased myocardial action.
 Blood levels of alcohol greater than 400 mg/dL can be fatal.

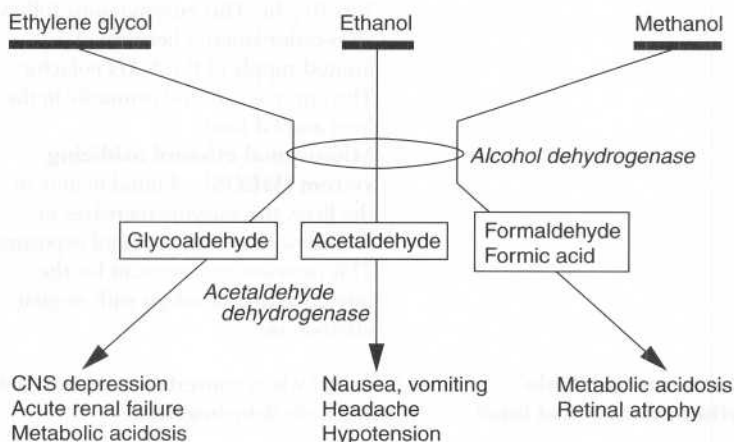


Figure 18–1. Toxic metabolites of alcohols. Ethanol, a preferred substrate for alcohol dehydrogenase, is used in methanol and ethylene glycol poisoning to slow the production of toxic metabolites from these alcohols.

What are the *chronic CNS* effects of alcoholism?

A deficiency of thiamine associated with chronic alcohol use can lead to Wernicke-Korsakoff syndrome. This disease is characterized by ophthalmoplegia, ataxia, and confusion.

What are the *chronic peripheral* effects of alcoholism?

Decreased liver function—Hepatitis and cirrhosis may develop.
GI irritation, inflammation, and bleeding
Gynecomastia and testicular atrophy in men due to the cirrhotic liver's inability to metabolize estrogen
Hypertension
Dilated cardiomyopathy
Although alcohol is not considered to be a direct carcinogen, alcohol consumption can lead to an increased risk of GI cancer.

Why is it unsafe for pregnant women to drink alcohol?

Ethanol use during pregnancy may lead to fetal alcohol syndrome, which includes mental retardation, growth deficiencies, microencephaly, and malformations of the face and head.

What are “the DTs”?

Delirium tremens—tremor, anxiety, tachycardia, delusions, and agitation. These symptoms are experienced by chronic alcohol users who are suddenly deprived of ethanol.

What is disulfiram used for?

Disulfiram, an **aldehyde dehydrogenase inhibitor**, is used adjunctively in some alcohol treatment programs. Patients who drink while taking disulfiram will experience nausea, hypotension, and vomiting. These adverse symptoms encourage avoidance of ethanol.

Which drugs are well known to cause a disulfiram-type reaction when used in conjunction with alcohol?

Metronidazole, the cephalosporins, and procarbazine

PHENCYCLIDINE (PCP)

What is it?

Phencyclidine or PCP, also known as “angel dust,” is a **dissociative anesthetic**

	(causing analgesia and catatonia without loss of consciousness) that blocks N-methyl, D-aspartic acid (NMDA) receptors (i.e., glutamate receptors). It is also a ketamine analogue.
What is this drug's mechanism of action?	It blocks serotonin (5-hydroxytryptamine [5-HT]) uptake.
What are the central physiologic actions of PCP?	PCP causes a schizophrenia-like psychosis involving distortion of time, space, and body image. Extremely high doses can cause seizures and coma.
What are the peripheral physiologic effects of PCP?	Increased blood pressure and heart rate Limb numbness Ataxia Hypersalivation Nystagmus

LSD

What is it?	Lysergic acid diethylamide
How does it work?	It interacts with 5-HT receptors in the midbrain.
What are the physiologic actions of LSD on the CNS?	Visual hallucinations and flashbacks Arousal Excitation Disturbed perception Disturbed mood Panic
What are the peripheral physiologic effects?	Mydriasis Tachycardia Flushing, lacrimation, salivation Increased blood pressure
What drug can block the hallucinatory effects of LSD?	Haloperidol

MARIJUANA

What is it?	Marijuana has as its active component Δ -9 THC (tetrahydrocannabinol), which is derived from the flowering tops of the hemp plant (<i>Cannabis sativa</i>).
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What are marijuana's effects on the CNS?	Sedation Euphoria Decreased psychomotor activity Impaired judgment, memory, and time sense
What peripheral physiologic effects does marijuana have?	Increased heart rate and blood pressure Injected (red) conjunctiva Dry mouth Bronchodilation Increased appetite
Does marijuana have any clinical indications?	Yes. Dronabinol is a pharmaceutical preparation of Δ -9 THC that is used to treat anorexia related to terminal conditions and as an antiemetic in chemotherapy.

COCAINE

What is cocaine's mechanism of action?	Cocaine blocks the reuptake of norepinephrine, serotonin, and dopamine (5-HT) into presynaptic nerve terminals. This blockade results in enhanced activity of these neurotransmitters.
What physiologic changes occur as a result of cocaine use?	Cocaine causes mydriasis, increases heart rate, alertness, and self confidence, and induces a temporary state of euphoria by stimulating the limbic system.
What are the signs of overdose?	Excitation Hallucinations and psychosis Seizures Respiratory depression Arrhythmias secondary to coronary vasospasm Coma
Does cocaine have any clinical use?	Yes—it is used as a local anesthetic and vasoconstrictor during ENT procedures.

OTHER DRUGS OF ABUSE

Are there additional drugs that can be abused?	Any drug has the potential for abuse. Only a few of the classic drugs of abuse have been mentioned in this chapter; others, such as caffeine, amphetamine,
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and nicotine, are discussed in detail in *Chapter 17—CNS Stimulants*. Also, benzodiazepines and opioids are each discussed separately in *Chapter 11—Anxiolytics, Hypnotics, and Sedatives* and *Chapter 19—Opioid Analgesics and Antagonists*.

COCOAINE

What is cocaine's mechanism of action?	Cocaine blocks the reuptake of norepinephrine, serotonin, and dopamine. It also blocks the breakdown of these neurotransmitters by inhibiting the enzymes MAO-A and MAO-B. This results in an accumulation of these neurotransmitters in the synaptic cleft, leading to an increase in their effects.
What pharmacologic effects does cocaine have as a result of cocaine's action?	Cocaine causes a rapid increase in heart rate and blood pressure. It also causes a decrease in respiratory rate and a decrease in body temperature. Cocaine also causes a feeling of euphoria and a loss of appetite.
What are the signs of cocaine toxicity?	Signs of cocaine toxicity include increased heart rate, increased blood pressure, increased body temperature, and decreased respiratory rate. Other signs include dilated pupils, dry mouth, and a feeling of restlessness.
How is cocaine toxicity treated?	Cocaine toxicity is treated with supportive care, including oxygen, fluids, and monitoring of vital signs. In severe cases, benzodiazepines may be used to sedate the patient.

OTHER DRUGS OF ABUSE

Are there additional drugs that can be abused?	Yes, there are many other drugs that can be abused, including alcohol, prescription drugs, and illicit drugs.
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19

Opioid Analgesics and Antagonists

What are opioids?

The term *opioid* refers to all agonists and antagonists with morphine-like activity as well as to naturally occurring and synthetic opioid peptides.

Give three examples of naturally occurring opioids.

1. Enkephalins
2. Endorphins
3. Dynorphins

Where do opioids act?

On the CNS—more specifically, on three main classes of opioid receptors:

1. Mu (μ) receptors
2. Kappa (κ) receptors
3. Delta (δ) receptors

These receptors are located throughout the CNS including the cortex, thalamus, brain stem, and spinal cord.

Describe the effects of μ , δ , and κ receptors.

μ receptors—Responsible for producing spinal/supraspinal analgesia, euphoria, respiratory depression, miosis, and constipation

κ receptors—responsible for producing spinal analgesia, sedation, dysphoria, and miosis.

δ receptors—responsible for producing supraspinal/spinal analgesia

Which drugs are considered full agonists?

Morphine
Meperidine
Methadone
Fentanyl
Heroin
Hydromorphone

Which drugs are considered partial agonists?	Codeine Propoxyphene Oxycodone Hydrocodone Buprenorphine These drugs in general produce less than maximal effect despite binding to all of the receptors.
Which drugs are considered mixed agonists/antagonists?	Pentazocine Nalbuphine Butorphanol These drugs are agonists at certain receptors and antagonists at others.
Which drugs are considered opioid antagonists?	Naloxone Naltrexone
How do all of these drugs differ in potency when compared to morphine?	See Table 19-1.

FULL AGONISTS

MORPHINE (Roxanol, MS Contin)

What is it?	A drug derived from the poppy plant, <i>Papaver somniferum</i> . It is the prototype opioid.
What receptors does morphine act on?	Morphine shows strong affinity for μ receptors and varying affinities for δ and κ receptors.
What are morphine's physiologic actions?	<p>Histamine and hormonal actions (increased prolactin, decreased GRH, CRH, CH, FSH, ACTH)</p> <p>Emesis</p> <p>Contraction of biliary smooth muscle and Cardiovascular changes—There is very little cardiovascular change at normal dosages; orthostatic hypotension, however, may occur.</p> <p>Decreased cough reflex, Decreased GI motility, and Depression of mental functioning (sedation)</p> <p>Respiratory depression—Fatalities can occur at high doses.</p>

Table 19–1. Opioid Analgesics: Comparison with Morphine

	Related Potency to Morphine	Duration of Analgesia
Fentanyl (Sublimaze)	80×	1–1.5 hr
Buprenorphine (Buprenex)	25–50×	4–8 hr
Hydromorphone (Dilaudid)	7×	4–5 hr
Butorphanol (Stadol)	5×	3–4 hr
Heroin (Diacetylmorphine)	3–5×	2–3 hr
Morphine (Roxanol, MS Contin)	1×	4–5 hr
Methadone (Dolophine)	1×	4–6 hr
Nalbuphine (Nubain)	1×	3–6 hr
Pentazocine (Talwin)	$\frac{1}{15}$ ×	3–4 hr
Oxycodone (Roxicodone)	$\frac{2}{3}$ ×	3–4 hr
Meperidine (Demerol)	$\frac{1}{10}$ ×	2–4 hr
Codeine	$\frac{1}{12}$ ×	3–4 hr
Propoxyphene (Darvon)	$\frac{1}{24}$ ×	4–5 hr

INCREASING POTENCY ↑

Euphoria**Analgesia**—Opioids are the most potent drugs available for relief of pain.**Miosis**Morphine gives you one
“HECk of a **DREAM.**”**What two physiologic effects of morphine are not affected by tolerance?**

Miosis and constipation

How is this drug used therapeutically?

Analgesia

Diarrhea

Relief of cough

Relief of acute pulmonary edema (past use)

What is the route of administration?	IV, po, sub-q, or IM
Describe the pharmacokinetics of morphine and most other opioids.	They are well absorbed orally (except for morphine), metabolized by the liver (usually to the glucuronide conjugates), and subsequently eliminated in urine.
Are there any adverse effects?	Yes. Respiratory depression—be particularly careful of this in patients with cor pulmonale, nausea, vomiting, elevation of intracranial pressure especially in head injury, urinary retention
What type of withdrawal symptoms are seen with opioids?	Chills Diarrhea Myalgia Agitation Anxiety
What is dextromethorphan?	A nonopioid derivative of morphine used as an anti-cough agent
What should I know about the other drugs discussed in this chapter?	They all produce physiologic effects and side effects similar to those of morphine; therefore, only special traits such as sites of action and unique characteristics are discussed. Remember that morphine is the classic opiate.

MEPERIDINE (Demerol)

What is the site of action?	This drug binds primarily to μ receptors.
What does meperidine do to the eyes?	It does not produce pinpoint pupils like other opiates, but rather causes the pupils to dilate because of its anticholinergic activity similar to that of atropine.
Describe the adverse effects.	Tremors Muscle twitches Rarely, convulsions
Name an important contraindication to meperidine use.	Never give meperidine or other opioids to patients on MAO inhibitors because this combination may result in severe respiratory depressions, hyperpyrexia, and convulsions.

What is loperamide (Imodium)?	A meperidine analogue used to treat diarrhea
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METHADONE (Dolophine)

What is the site of action?	This drug exerts its greatest actions on the μ receptors.
How is methadone administered?	Orally
What is its therapeutic use?	Narcotic detoxification: Because of its long half life, methadone can prevent an addict from suffering severe withdrawal symptoms as the body normalizes.

FENTANYL (Sublimaze)

Describe this drug and its site of action.	Fentanyl is a synthetic opioid agonist active at the μ receptors.
How is fentanyl used therapeutically?	For anesthesia—alone or in combination with droperidol For chronic and postoperative pain
How is fentanyl administered?	IV or transdermally
What are the adverse effects?	Apnea/hypoventilation CNS depression Muscular rigidity

HEROIN (Diacetylmorphine)

What are the pharmacologic properties of heroin?	Heroin is hydrolyzed into morphine and therefore has properties similar to morphine's. Heroin is, however, more lipid-soluble and crosses the blood-brain barrier more quickly than does morphine.
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HYDROMORPHONE (Dilaudid)

State this agonist's site of action.	The μ receptors
How is it used therapeutically?	For moderate pain

PARTIAL AGONISTS**CODEINE**

What is the site of action?	Codeine has low affinity for μ receptors.
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Describe its pharmacologic actions. Codeine resembles morphine pharmacologically but has milder actions.

How is this drug used therapeutically? As an antitussive and to relieve mild-to-moderate pain

PROPOXYPHENE (Darvon)

Where is the site of action? At the μ receptors

How is propoxyphene used therapeutically? For analgesia

Are there adverse effects? Convulsions and hepatotoxicity

HYDROCODONE (Hydrocan)

Describe this agonist's site of action. The μ receptors

What are the adverse effects? Histamine release

OXYCODONE (Roxicodone)

What is this agonist's site of action? The μ receptors

Are there any adverse effects? The adverse effects are similar to those of morphine.

BUPRENORPHINE (Buprenex)

Where is the site of action? Buprenorphine is a partial μ agonist.

How does buprenorphine function? It dissociates from the μ receptors *slowly*, which may contribute to its long duration of action and low physical dependence.

Describe this drug's therapeutic indications. Analgesia in postoperative patients
Relief of moderate to severe pain

What are the adverse effects? Similar to those of morphine—respiratory depression, sedation, and nausea and vomiting

MIXED AGONISTS/ANTAGONISTS**PENTAZOCINE (Talwin)**

Describe how this drug functions at its dual sites of action. It acts as an agonist at κ and δ an antagonist at μ and δ receptors.

What are its therapeutic uses? Analgesia—relief of moderate to severe pain

Are there adverse effect? Psychotomimetic effects (anxiety, nightmares)

NALBUPHINE (Nubain)

Describe how this drug functions at its dual sites of action. It acts as an agonist at the κ receptors and an antagonist at the μ receptors.

What are the therapeutic uses? Analgesia—relief of moderate to severe pain

Are there any adverse effects? Histamine release

BUTORPHANOL (Stadol)

How does this drug function at its dual sites of action? It acts as an agonist at the κ receptors and as a weak antagonist at the μ receptors.

Is there a therapeutic use? Acute pain relief

What are the adverse effects? Drowsiness
Weakness
Sweating
Nausea

OPIOID ANTAGONISTS**NALOXONE (Narcan)**

How does this drug work? Naloxone binds all opioid receptors to displace bound opioid agonists.

How is naloxone used therapeutically? It reverses the respiratory depression and coma of opioid overdose.

How quickly does it work? Within 30 seconds of IV injection

What is naloxone's duration of action?	One to two hours—This is important because <i>patients may relapse into respiratory depression and coma if repeated dosages of naloxone are not given!</i>
Are there adverse effects?	Tachycardia and arrhythmias
NALTREXONE (Trexan)	
Describe this drug's mechanism of action.	Naltrexone binds at all opioid receptors.
What is naltrexone's therapeutic use?	It is beneficial for treating opioid dependency because it has a longer duration of action than naloxone.
List the adverse effects.	Hepatotoxicity Nausea Sedation Headache
What happens if naloxone or naltrexone is given in the absence of an opioid agonist?	At most doses there is no physiologic effect if an opioid agonist is not present.

Section IV

Cardiovascular System

Cardiovascular
System

Section IV

20

Antihypertensive Drugs

Define hypertension.

Persistent diastolic blood pressure greater than 90 mm Hg and systolic pressure greater than 140 mm Hg

How can hypertension be categorized?

Into three stages:

Stage 1, Mild—Systolic BP 140–159 or diastolic BP 90–99

Stage 2, Moderate—Systolic BP 160–179 or diastolic BP 100–109

Stage 3, Severe—Systolic BP > 180 or diastolic BP > 110

What causes hypertension?

Of patients who have hypertension, 90% have what is known as essential hypertension (i.e., the etiology is unknown). The other 10% have hypertension secondary to other diseases such as renal artery stenosis, pheochromocytoma, Cushing's disease, and coarctation of the aorta. Environmental factors such as sodium intake, obesity, and smoking can also cause hypertension.

What is the most common presenting sign of hypertension?

There is none! When patients are first diagnosed, they are usually asymptomatic.

What are some of the potential complications of hypertension?

Coronary artery disease, cardiac and renal failure, and stroke

What is the hydraulic equation for blood pressure?

$\text{Cardiac output} \times \text{total peripheral vascular resistance} = \text{blood pressure}$

What conclusions can be drawn from this equation?

Drugs that reduce either cardiac output (CO) or peripheral vascular resistance (PVR) will produce a reduction in blood pressure.

What are the major classes of drugs used to treat hypertension?

Sympatholytic agents—Methyldopa, clonidine, guanfacine, α blockers, β -blockers, ganglionic blockers, and postganglionic adrenergic neuronal blockers. All of these agents reduce peripheral vascular resistance or cardiac output.

Diuretics—Loop and thiazides diuretics are the most important agents of this antihypertensive drug class. They reduce blood volume, which in turn reduces cardiac output.

Vasodilators—Hydralazine, minoxidil, sodium nitroprusside, diazoxide, and calcium channel blockers. These agents reduce PVR.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists—Captopril, enalapril, lisinopril, and losartan. These drugs reduce PVR; however, they also reduce blood volume by reducing the secretion of aldosterone.

Figure 20–1 shows the sites of action of the major classes of antihypertensive drugs.

SYMPATHOLYTIC AGENTS

CENTRALLY ACTING ANTIHYPERTENSIVES

Methyldopa (Aldomet)

What is this drug's mechanism of action?

Methyldopa stimulates central presynaptic α_2 -adrenergic receptors and inhibits the release of norepinephrine.

What is its primary effect?

The decreased sympathetic outflow results in decreased peripheral vascular resistance. It also creates some reduction in cardiac output.

What is the route of administration?

Oral or intravenous

What is the clinical indication for methyldopa?

Moderate hypertension. Methyldopa is often given in combination with a thiazide diuretic.

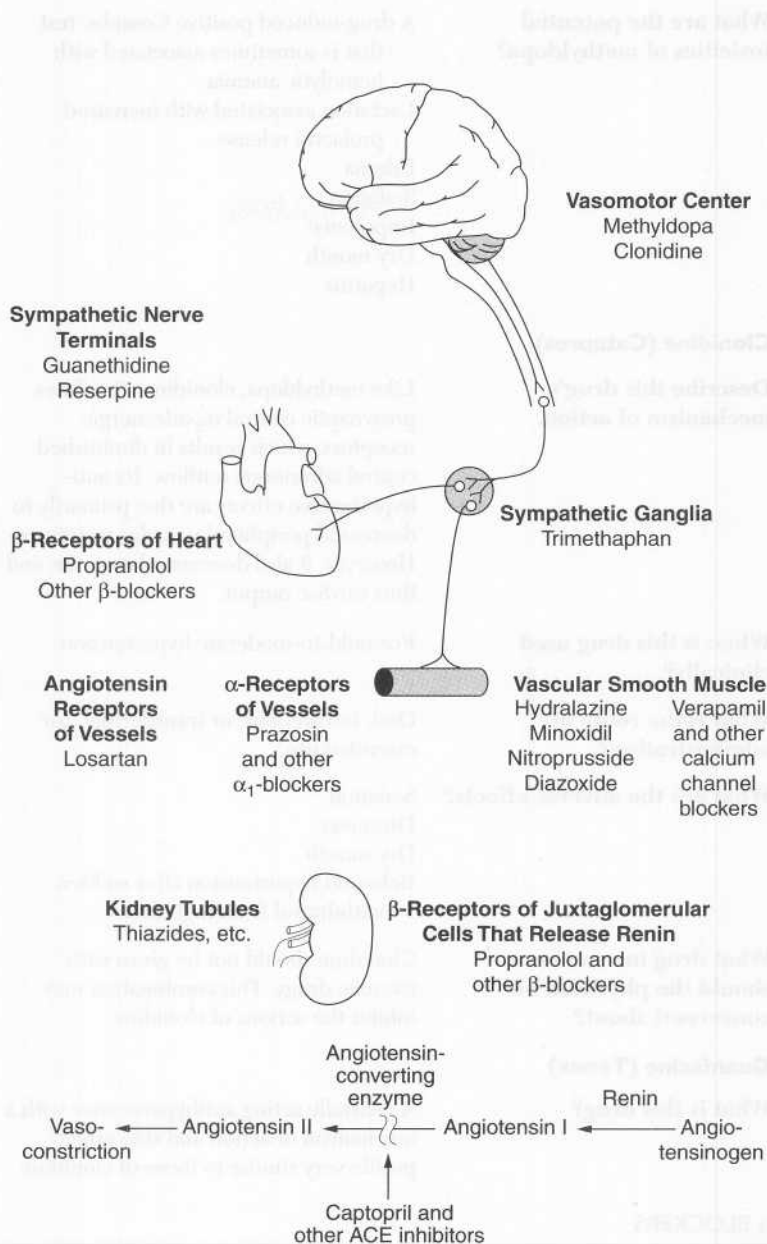


Figure 20-1. Sites of action of the major classes of antihypertensive drugs. (Redrawn from Katzung BG: *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1998.)

What are the potential toxicities of methyldopa?

A drug-induced positive Coombs' test that is sometimes associated with hemolytic anemia
Lactation associated with increased prolactin release
Edema
Sedation
Impotence
Dry mouth
Hepatitis

Clonidine (Catapres)

Describe this drug's mechanism of action.

Like methyldopa, clonidine stimulates presynaptic central α_2 -adrenergic receptors, which results in diminished central adrenergic outflow. Its anti-hypertensive effects are due primarily to decreased peripheral vascular resistance. However, it also decreases heart rate and thus cardiac output.

When is this drug used clinically?

For mild-to-moderate hypertension

What is the route of administration?

Oral, intravenous, or transdermal (for extended use)

What are the adverse effects?

Sedation
Dizziness
Dry mouth
Rebound hypertension after sudden withdrawal from high doses

What drug interactions should the physician be concerned about?

Clonidine should not be given with tricyclic drugs. This combination may inhibit the actions of clonidine.

Guanfacine (Tenex)

What is this drug?

A centrally acting antihypertensive with a mechanism of action and side effect profile very similar to those of clonidine

α BLOCKERS

For more information on α blockers, see *Chapter 9—Adrenergic Antagonists*.

Give some examples of α -adrenergic blockers.

Prazosin (Minipress)
Terazosin (Hytrin)
Doxazosin (Cardura)

How do they work?	They block the α_1 -adrenergic receptors.
What are the antihypertensive effects of these drugs?	The antihypertensive effects are mainly related to a decrease in peripheral vascular resistance. These drugs exert minimal effects on cardiac output.
Describe the clinical use for α-blockers.	Moderate hypertension
What are the adverse effects of prazosin and its synthetic analogues?	Dizziness Orthostatic hypotension—especially after the first dose Headache

β BLOCKERS

For more information on β blockers, see *Chapter 9—Adrenergic Antagonists*.

Give some examples of β blockers.	Propranolol Metoprolol Atenolol Labetalol Carvedilol (Coreg)
Describe the mechanism of action.	Blockade of β_1 - and β_2 -adrenergic receptors
What is the clinical use?	A β blocker is often one of the first-line agents chosen to treat patients with mild-to-moderate hypertension. These drugs may be of particular use in high renin states because they reduce renin release. See Figure 20-2.
What are the adverse effects?	Sedation Fatigue Bronchoconstriction Impotence May decrease HDL and increase plasma triacylglycerol

GANGLIONIC BLOCKERS

See *Chapter 7—Cholinergic Antagonists* for more information on ganglionic blockers.

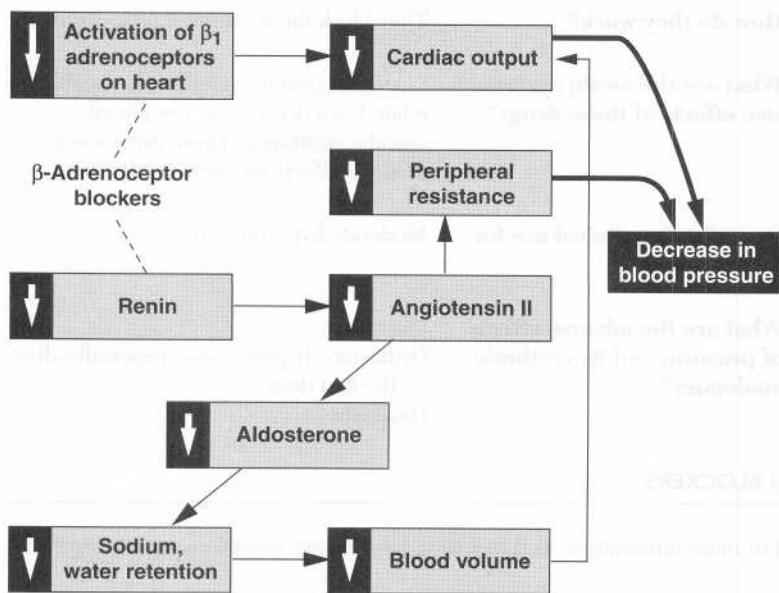


Figure 20-2. Actions of β -adrenergic blocking agents. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 184.)

Give two examples of ganglionic blockers.

Trimethaphan and hexamethonium

What is their clinical use?

These agents are no longer used to treat hypertension because of their severe adverse effects. They are mentioned here because they are tested on the USMLE.

Describe the adverse effects.

Parasympathetic blockade (urinary retention, blurred vision, and so forth) as well as sympathetic blockade (sexual dysfunction and orthostatic hypotension).

POSTGANGLIONIC ADRENERGIC NEURONAL BLOCKERS

See Chapter 9—*Adrenergic Antagonists* for more information on these agents.

Give two examples.

Reserpine and guanethidine

What is the mechanism of action?

These drugs block the release of stored norepinephrine.

Describe their clinical role in hypertension.

Both are rarely used to treat hypertension because of low efficacy and significant adverse effects.

DIURETICS

See Chapter 23—*Diuretics* for additional information on diuretics.

What types of diuretics are chosen most frequently to control hypertension?

Although all oral diuretics can be used to treat hypertension, the most frequently chosen are thiazide and loop diuretics because they are the most effective.

How are diuretics used therapeutically?

For mild-to-moderate hypertension

What are some of the toxic effects of diuretics?

Potassium depletion—most common effect
Possible impairment of glucose tolerance
Possible increase in plasma lipid concentrations

VASODILATORS

HYDRALAZINE (Apresoline)

Describe this drug's mechanism of action.

Direct vasodilation of **arteriolar** smooth muscle, which results in decreased PVR. This reduction in resistance is usually followed by reflex tachycardia and fluid retention. β blockers are often co-administered to minimize the sympathetic effects.

How is hydralazine used clinically?

For moderate hypertension and CHF

What are the adverse effects?

Lupus-like syndrome (☞ board question)
Cardiovascular effects—hypotension, reflex tachycardia, palpitations, angina
Headache
Nausea
Diarrhea

MINOXIDIL (Loniten)

What is this drug's mechanism of action?

Minoxidil is a potent **arterial** vasodilator that works by opening potassium

channels, which results in hyperpolarization and relaxation of smooth muscle cells.

How is minoxidil used clinically?

For severe hypertension
For hair replacement (Rogaine)
As with hydralazine, minoxidil is often administered with β blockers and diuretics.

Describe the adverse effects.

Edema due to sodium and water retention
Reflex tachycardia
Flushing
Headache
Hypertrichosis (increased hair growth)

SODIUM NITROPRUSSIDE

Describe its mechanism of action.

Sodium nitroprusside releases nitric oxide, which stimulates the enzyme guanylyl cyclase and increases production of intracellular cyclic guanosine monophosphate (cGMP) concentrations. This results in a decrease in intracellular calcium ions and consequent vascular smooth muscle relaxation (both arterial and venous).

How is sodium nitroprusside used clinically?

For hypertensive emergencies and CHF

What is the route of administration?

Intravenous

What are the adverse effects?

Hypotension
Metabolic acidosis
Cyanide toxicity—This may occur as a result of cyanide ions produced during metabolism of sodium nitroprusside. (Cyanide toxicity can be treated with an infusion of rhodanese, an enzyme that combines cyanide and thiosulfate to produce thiocyanate, a less toxic metabolite.)
Thiocyanate toxicity—Symptoms include weakness, psychosis, muscle spasms, and convulsions.

DIAZOXIDE

What is its major mechanism of action?	Diazoxide prevents arterial smooth muscle contraction by opening potassium channels and stabilizing membrane potentials.
What other action does this drug have?	It prevents insulin release from the pancreas.
State the route of administration.	IV
How is diazoxide used clinically?	For hypertensive emergencies
What are this drug's adverse effects?	Hypotension Reflex tachycardia Hyperglycemia

CALCIUM CHANNEL BLOCKERS

See *Chapter 22—Drugs Used to Treat Congestive Heart Failure* for additional information on calcium channel blockers.

Give three examples of calcium channel blockers.	Nifedipine, verapamil, and diltiazem
Describe the mechanism of action.	Inhibition of calcium influx into smooth muscle cells. Nifedipine is the most selective for the peripheral vasculature.
What are the adverse effects of these drugs?	Constipation Headache Dizziness

ACE INHIBITORS

What are they?	ACE inhibitors are angiotensin-converting enzyme inhibitors.
Which physiologic system are ACE inhibitors effective against?	The renin-angiotensin-aldosterone system
Explain this system.	Renin is an enzyme that acts on the substrate angiotensinogen and converts it to angiotensin I, which is then converted

to angiotensin II in the lungs by ACE (peptidyl-dipeptidase A). Angiotensin II is a potent vasoconstriction and stimulates the release of aldosterone. Figure 20-3 shows the relationship between the angiotensinogen and kininogen systems.

Give some examples of ACE inhibitors.

Captopril (Capoten)—prototype
 Lisinopril (Prinivil, Zestril)
 Enalapril (Vasotec)
 Benazepril (Lotensin)

How do they work?

ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also increase levels of bradykinin, which is a

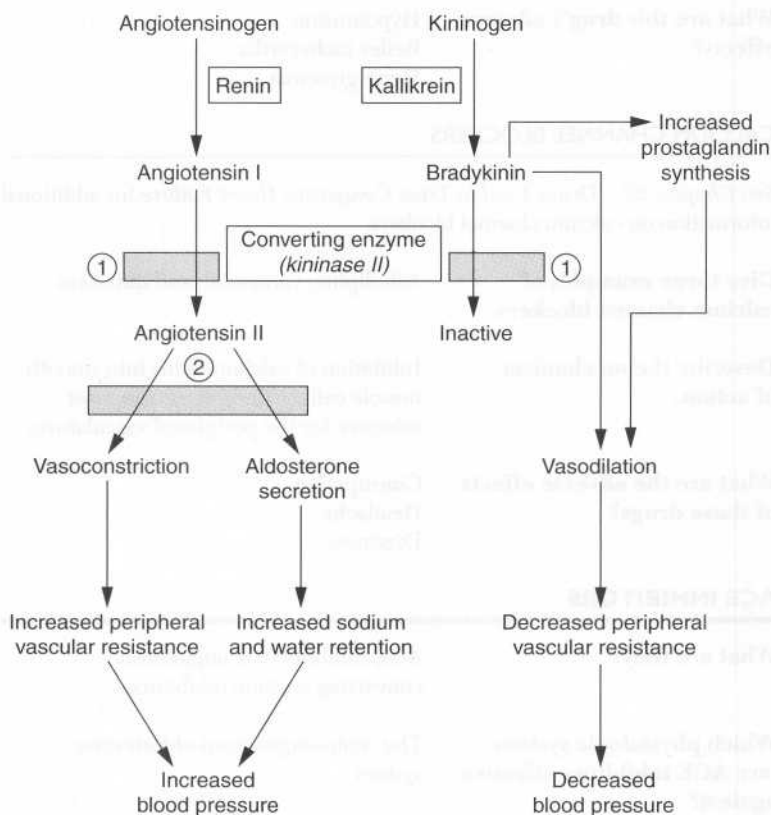


Figure 20-3. Sites of action of ACE inhibitors and receptor blockers. ① = Site of ACE blockade. ② = Site of receptor blockade. (Redrawn from Katzung BG: *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1998.)

For what conditions does a physician prescribe ACE inhibitors?

potent vasodilator (see Figure 20–3). These drugs do not have much of an effect on cardiac output and heart rate.

Mild-to-moderate hypertension
CHF (vasodilatory effects)
Diabetic nephropathy

Describe the absorption of captopril.

It is well absorbed orally. It does not enter the CNS.

How is captopril eliminated?

Elimination occurs primarily through the urine.

What are the adverse effects of ACE inhibitors?

Dizziness
Cough
Angioedema
Hyperkalemia
Sudden drop in blood pressure after an initial dose—This can occur in patients who are hypovolemic.
Renal failure in patients who have bilateral renal artery stenosis
Proteinuria
Neutropenia (rare)

Should ACE inhibitors be administered to pregnant women?

No! In the second and third trimesters there is a risk of fetal hypotension, anuria, and malformations.

What drug interactions should physician's monitor while administering ACE inhibitors?

Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the vasodilatory effects of ACE inhibitors, because NSAIDs block the actions of bradykinin.

ANGIOTENSIN II RECEPTOR ANTAGONISTS: LOSARTAN (COZAAR) AND VALSARTAN (Diovan)

Describe the mechanism of action of these drugs.

They block angiotensin II at its receptor site, thus inhibiting both the vasoconstriction and aldosterone-secreting effects of angiotensin II. They do not affect the bradykinin system.

What is the route of administration?

Oral

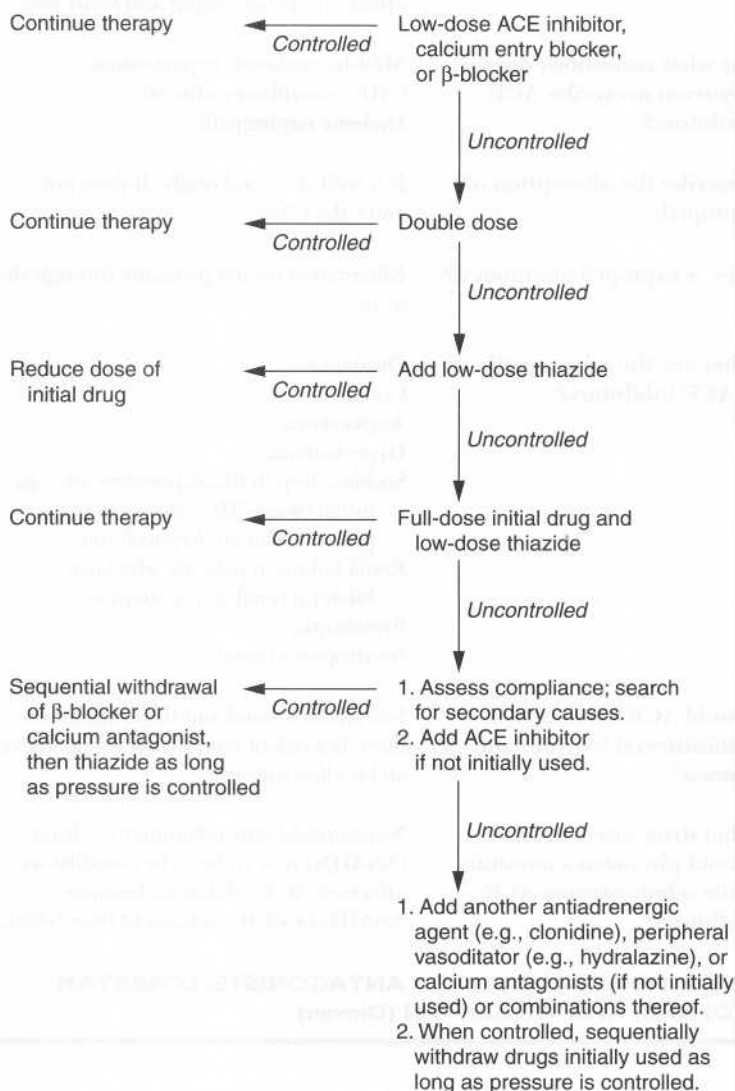


Figure 20-4. Schematic approach to the treatment of the patient with hypertension in whom a specific form of therapy is not indicated and volume expansion is not present. (Redrawn from Fauci AS, Braunwald E, Isselbacher KJ et al: *Harrison's Principles of Internal Medicine*, 14th ed. New York, McGraw-Hill, 1997.)

How are these drugs used clinically?

For mild-to-moderate hypertension

Name three adverse effects of losartan and valsartan.

1. Headache
2. Hyperkalemia—especially in patients taking potassium-sparing diuretics
3. Hypotension

What are the contraindications?

Like the ACE inhibitors, losartan and valsartan are contraindicated in pregnancy because they may cause fetal malformations, anuria, and hypotension.

SUMMARY

How do physicians choose which antihypertensive medications to use?

Unless the patient has severe hypertension, a single agent will be used initially—usually a diuretic, β -adrenergic blocker, or ACE inhibitor. The specific choice will depend upon the patient's other medical conditions. If the hypertension remains uncontrolled, other agents will be added in a stepwise fashion (Figure 20-4).

What is malignant hypertension?

Hypertension with associated vascular damage (i.e., hypertensive encephalopathy, retinal hemorrhage)

How is this condition treated?

In the initial stages, intravenous antihypertensive agents such as diazoxide and sodium nitroprusside are used. The goal is not normalization of blood pressure but rather a 25% reduction, because sudden hypoperfusion may result in brain injury. Excess fluid may be removed with loop diuretics or, if necessary, dialysis.

21

Antiarrhythmic Drugs

What is an arrhythmia?

In a normal heart, an impulse originates in the SA node, travels through the atrial muscle into the AV node, through the Purkinje system, and down to the ventricular muscle. Any rhythm that does not start at the SA node or that is not under the usual autonomic control is defined as an arrhythmia.

Why are cardiac arrhythmias significant?

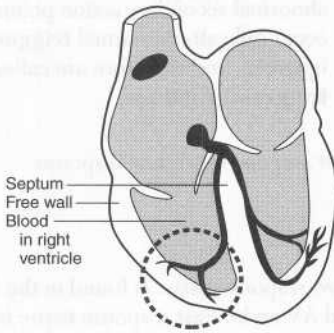
Cardiac arrhythmias are the No. 1 cause of death in the U.S. after myocardial infarction (📌 board question).

How do arrhythmias form?

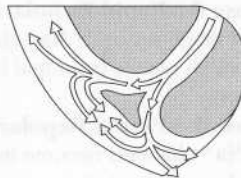
In one of three ways:

1. **Reentry**—This is the most common cause of arrhythmias (Figure 21-1). The reentry phenomenon occurs when myocardial injury blocks a normally viable conduction pathway. An action potential, once initiated, is usually conducted through several different pathways to the rest of the myocardium; however, if one of the pathways is blocked, then by the time the impulse travels through the damaged pathway, the surrounding cells may be in a resting state and ready to be depolarized. If this is the case, then reexcitation of the cardiac tissue will occur.
2. **Enhanced automaticity**—Normally the SA node sets the pace for the heart. If other areas of the heart begin to depolarize more quickly than the SA node, an arrhythmia may result.
3. **Triggered automaticity**—On occasion (during ischemia digitalis

A. Conduction System

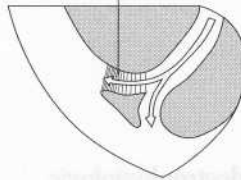


B. Normal Conduction



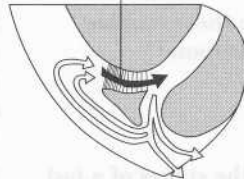
C. Unidirectional Block and Reentry

Forward impulse obstructed and extinguished

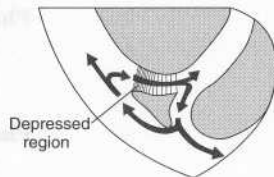


1. Decremental conduction and unidirectional block of antegrade impulse

Retrograde impulse



2. Retrograde impulse conducted across depressed region



3. Reentry circuit established

Figure 21-1. Schematic drawings of the heart showing unidirectional block and reentry the most common cause of arrhythmias. (A) Conduction system. Circled area (enlarged in the other drawings) shows small bifurcating twig of the Purkinje system where it enters the ventricular wall. (B) The normal passage and fate of an impulse that is conducted down the twig. It splits into two impulses at the bifurcation, and these collide (and extinguish each other) after exciting the ventricular muscle. (C) The sequence of events when the normal impulse finds an areas of unidirectional block (blocked depressed region) in one of the branches. As shown by the path of the impulse in the depressed region (1), this weak stimulus is unable to conduct through or to jump over the area of block. In contrast, the wave in the undepressed branch is able to excite the entire ventricular wall (2). Because the ventricular wall constitutes a large mass of cells, the strong ventricular depolarization is able to jump the depressed region and results in a retrograde impulse (shown by the black arrows in 2 and 3). The retrograde impulse may be propagated if the impulse finds excitable tissue, i.e., the refractory period is shorter than the conduction time. This impulse will then reexcite tissue it had previously passed through, and a reentry arrhythmia will be established in the circuit (indicated by the black arrows in 3). (Redrawn from Katzung BG: *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT, Appleton & Lange, 1998, p 225.)

intoxication, or adrenergic stress), a normal cardiac action potential may be interrupted or followed by an abnormal depolarization. These abnormal secondary action potentials occur only after a normal **triggering** upstroke, and therefore are called **triggered rhythms**.

From an electrophysiologic standpoint, what are the two types of cardiac tissue?

Fast response and slow response

Where are these cardiac tissue types found?

Slow response tissue is found in the SA and AV node. Fast response tissue is found in the myocardium and Purkinje cells.

Describe the stages of a fast response cardiac action potential.

Phase 0—Rapid Depolarization—

Voltage-sensitive Na^+ channels open, which results in a rapid influx of Na^+ ions.

Phase 1—Partial Repolarization—

Na^+ channels become inactivated; K^+ channels begin to open, which results in an efflux of K^+ and Cl^- influx.

Phase 2—Plateau— Ca^{2+} influx and K^+ efflux causes a plateau, which is unique to the cardiac action potential.

Phase 3—Rapid Repolarization— K^+ efflux and inactivation of Ca^{2+} channels

Phase 4—Diastolic Depolarization—

The resting membrane potential is maintained by K^+ efflux and slow Na^+ and Ca^{2+} influx (Figure 21-2).

How does a slow response cardiac action potential differ from a fast response action potential?

SA and AV nodes have a slow upstroke velocity, a smaller magnitude of action potential, and a brief plateau. There are no fast Na^+ channels, and the action potential is caused by the opening of Ca^{2+} channels (see Figure 21-2).

What are some examples of supraventricular arrhythmias?

Atrial fibrillation, atrial flutter, and multifocal atrial tachycardia

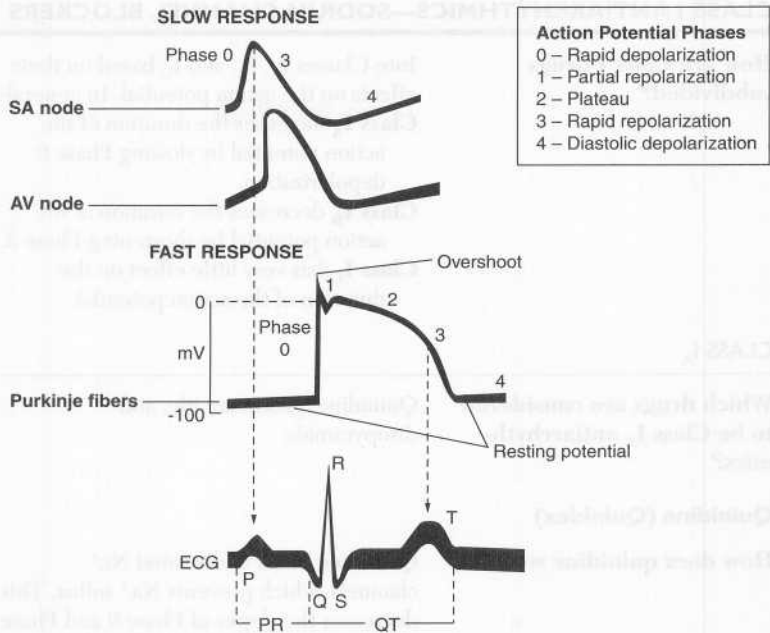


Figure 21-2. Schematic representation of normal cardiac action potentials from different tissues in the heart and their relationship to a standard ECG.

What are some examples of ventricular arrhythmias?

Ventricular tachycardia, ventricular fibrillation, and premature ventricular contractions

Generally, what is the mechanism of action of the antiarrhythmic drugs?

Suppression of arrhythmias by blocking either autonomic function or specific ion channels

What are the four classes of antiarrhythmic drugs?

Class I—sodium channel blockers
 Class II— β -adrenergic blockers
 Class III—potassium channel blockers
 Class IV—calcium channel blockers
 Some drugs, such as sotalol and amiodarone, will exhibit properties of more than one class. Other drugs, such as digoxin and magnesium sulfate, do not belong to a particular class.

CLASS I ANTIARRHYTHMICS—SODIUM CHANNEL BLOCKERS

How are Class I drugs subdivided?

Into Classes I_A, I_B, and I_C based on their effects on the action potential. In general:

Class I_A increases the duration of the action potential by slowing Phase 0 depolarization.

Class I_B decreases the duration of the action potential by shortening Phase 3.

Class I_C has very little effect on the duration of the action potential.

CLASS I_A

Which drugs are considered to be Class I_A antiarrhythmics?

Quinidine, procainamide, and disopyramide

Quinidine (Quinidex)

How does quinidine work?

Quinidine binds to activated Na⁺ channels, which prevents Na⁺ influx. This decreases the slopes of Phase 0 and Phase 4. Thus, tissues that are frequently depolarizing will be selectively suppressed over tissues that are depolarizing at a normal frequency. This drug property is termed **use-dependent block**. Quinidine also inhibits K⁺ currents and increases repolarization time.

What are the clinical indications for administration of quinidine?

Ventricular tachycardia and supraventricular arrhythmias (most commonly, atrial fibrillation and atrial flutter)

What are its effects on ECG?

Quinidine prolongs the QT interval.

How is this drug administered?

Orally

Where is it metabolized?

In the liver—half-life of 6 to 8 hours

What are the adverse effects of quinidine?

Noncardiac:

GI—Diarrhea, nausea, and vomiting are commonly observed.

Possible cinchonism—a symptom

complex that includes blurred vision, dizziness, headache, and tinnitus
 Quinidine syncope, characterized by recurrent lightheadedness and episodes of fainting
 Thrombocytopenic purpura

Cardiac:

Torsade de pointes—a type of arrhythmia with prolongation of the QT interval
 Proarrhythmogenic effects—AV block or asystole

Are there drug interactions?

Quinidine increases plasma levels of digoxin and oral anticoagulants. Pheno-barbital and phenytoin reduce quinidine plasma levels.

Procainamide (Pronestyl)

What are the therapeutic indications for procainamide?

It is used for treating both ventricular and supraventricular arrhythmias as well as premature ventricular contractions.

Describe the metabolite of procainamide.

A portion of procainamide is metabolized in the liver to *N*-acetyl procainamide (NAPA), which has the properties of a Class III drug. This metabolite may cause torsade de pointes.

How is procainamide administered?

Orally, intravenously, or intramuscularly

What are the adverse effects?

Lupus-like syndrome (☞ common board question)—Initially, this drug-induced lupus will manifest as a rash and small-joint arthralgia. Renal involvement is unusual.
 Pleuritis and pericarditis can also occur.
 Toxic effects can cause asystole, hallucination, and psychosis.
 Torsade de pointes

Disopyramide (Norpace)

Describe this drug's mechanism of action.

Very similar to quinidine except that it produces a greater negative inotropic effects and possesses stronger anticholinergic effects

How is disopyramide administered?	IV or PO
In what clinical situations is disopyramide used?	It can be used for treating both ventricular and supraventricular arrhythmias.
Describe the metabolism of this drug.	It is largely excreted in the urine unchanged.
What adverse effects should you watch for?	Anticholinergic effects—Dry mouth, urinary retention Constipation, precipitation of glaucoma Torsade de pointes Heart failure in patients who have left ventricular dysfunction Prostatism

CLASS I_B

Which drugs are considered Class I_B antiarrhythmics?	Lidocaine Tocainide Mexiletine Phenytoin
Lidocaine (Xylocaine)	
What ion channels does lidocaine affect?	Lidocaine blocks both activated and inactivated Na ⁺ channels, but exerts greater effects on inactivated channels. It also decreases the slopes of Phases 0 and 4.
When do you use this drug?	Lidocaine is the drug of choice for acute management of ventricular arrhythmias. It is also used as a local anesthetic.
How is lidocaine administered?	Intravenously
Describe the metabolism of lidocaine.	Hepatic—Dosage must be adjusted in patients who have hepatic dysfunction.
What are the ECG effects?	Usually there is no change in PR or QRS interval duration.
Are there side effects to monitor during administration?	CNS effects—Drowsiness, numbness, slurred speech, and convulsions; nystagmus is an early sign of toxicity.

Tocainide (Tonocard)

What are the therapeutic indications?

Tocainide is used primarily for treating ventricular arrhythmias.

How is it administered?

Orally

What are this drug's adverse effects?

Cardiovascular effects—bradycardia, tachycardia, AV block, hypotension, ventricular tachycardia
Anorexia, nausea
Tremor
Pulmonary fibrosis (rare)
Bone marrow aplasia (rare)

Mexiletine (Mexitil)

What is this drug's clinical use?

It is used to treat ventricular arrhythmias.

How is mexiletine administered?

Orally

What toxicities are important to remember when using mexiletine?

Dizziness, nervousness
Nausea and vomiting
Blood dyscrasias
Nystagmus, thrombocytopenia
Leukopenia, agranulocytosis

Phenytoin (Dilantin)

How is this drug classified?

Phenytoin is an anticonvulsant that binds to inactivated Na^+ channels and prolongs the inactivated state.

What is the route of administration?

IV or PO

State the therapeutic indications.

Drug of choice for treating digoxin-induced atrial and ventricular arrhythmias

Are there adverse effects?

CNS effects—nystagmus, ataxia
Gingival hyperplasia
Serious bone marrow and dermatologic reactions can occur.

CLASS I_C

State three drugs considered to be Class I_C antiarrhythmics.

1. Flecainide
2. Propafenone
3. Moricizine

Flecainide (Tambocor)

How does this drug work?

Flecainide blocks Na^+ channels in Purkinje cells, which shortens action potential duration. It also blocks K^+ channels in ventricular myocytes, which prolongs the action potential. The net effect is minimal change in action potential duration.

When is flecainide used?

For treating life-threatening supraventricular and ventricular arrhythmia in patients without myocardial structural abnormalities

What toxicities are associated with flecainide?

Proarrhythmic effects—The cardiac arrhythmia suppressor trial (CAST) study showed that flecainide increased mortality in patient who recently suffered an MI and who had asymptomatic ventricular arrhythmias. Therefore, it is used only as a last-line agent.

CNS effects—blurred vision, headache
Heart block in patients who have conduction system disease

Propafenone (Rythmol)

How is this drug used clinically?

For treating supraventricular and ventricular arrhythmias

What is its mechanism of action?

Propafenone possesses a mechanism of action similar to that of flecainide, but it exerts some β -adrenergic blockade activity as well.

State the adverse effects.

Proarrhythmic effects
 β blockade effects (bronchospasm, bradycardia)

Moricizine (Ethmozine)

How does moricizine work?

Its mechanism of action is similar to that of flecainide.

How is this drug used clinically?

Moricizine is used for treatment of ventricular arrhythmias.

What are the adverse reactions?

Proarrhythmic effects

CLASS II ANTIARRHYTHMICS— β BLOCKERS

See Chapter 9—Adrenergic Antagonists for a more detailed discussion of these agents.

Give some examples of drugs in this group. Sotalol, propranolol, and esmolol. Sotalol also exhibits Class III properties.

At which part of the action potential do these drugs work? Class II drugs work at diminishing Phase 4, thus depressing automaticity and decreasing heart rate.

SOTALOL

What is its mechanism of action? Sotalol decreases automaticity, slows AV nodal conduction, and prolongs the AV refractory period by both K^+ channel blockade and blockade of β -adrenergic receptors.

How is this drug used clinically? It is used to treat ventricular tachyarrhythmias and supraventricular arrhythmias.

ESMOLOL

When is this drug used? Esmolol is a very short acting β -adrenergic blocker and is almost always used in the treatment of acute surgical arrhythmias.

CLASS III ANTIARRHYTHMICS—POTASSIUM CHANNEL BLOCKERS

Which drugs fall into this category? Bretylium and amiodarone

BRETYLIUM

State the mechanism of action for bretylium. It prolongs the ventricular action potential and effective refractory period. It also blocks norepinephrine release.

Describe this drug's clinical use. Bretylium is used for treating refractory ventricular fibrillation and ventricular tachycardia during times of cardiac arrest.

What are the adverse effects? Postural hypotension

AMIODARONE (Cordarone)

What is it?	A drug structurally related to thyroid hormone
Describe its mechanism of action.	Amiodarone exhibits properties of Class I to IV drugs, but predominantly has Class III actions.
What are its clinical uses?	This drug is used for treating refractory atrial flutter/fibrillation and ventricular tachyarrhythmia.
How is amiodarone administered?	Orally or IV
What are the adverse effects of amiodarone?	<p>Interstitial pulmonary fibrosis</p> <p>CNS—tremor, ataxia</p> <p>Hepatocellular necrosis</p> <p>Photosensitivity</p> <p>Corneal microdeposits</p> <p>Thyroid dysfunction (hypo- or hyperthyroidism)</p> <p>Blue skin discoloration caused by iodine accumulation</p> <p>Because of these side effects, patients will often have liver function tests (LFTs), pulmonary function tests (PFTs), and thyroid function tests (TFTs) checked prior to initiating treatment.</p>

CLASS IV ANTIARRHYTHMICS—CALCIUM CHANNEL BLOCKERS

Which drugs belong to this group?	Verapamil, diltiazem, and nifedipine
How do they work?	<p>These drugs block “L”-type calcium channels and decrease both SA node automaticity and AV nodal conduction.</p> <p>Verapamil has the greatest effect on cardiac tissue.</p>
What types of arrhythmias are treated with calcium channel blockers?	Supraventricular arrhythmias (atrial flutter, atrial fibrillation)

What are the major side effects of calcium channel blockers?

Bradycardia
CHF
Hypotension
Dizziness
Constipation

For more information on calcium channel blockers, see *Chapter 20—Antihypertensive Drugs*.

OTHER ANTIARRHYTHMIC AGENTS

DIGOXIN (Lanoxin)

How does this drug work?

Digoxin inhibits the Na^+/K^+ ATPase pump in myocardial cell membranes, thereby increasing the exchange of intracellular Na^+ for extracellular Ca^{2+} by the $\text{Na}^+/\text{Ca}^{2+}$ exchanger.

How does digoxin serve as an antiarrhythmic?

It increases the refractory period and decreases the conduction time of the AV node.

How is digoxin used therapeutically?

For treating supraventricular arrhythmias and congestive heart failure

What are the toxicities to watch for?

Atrial or ventricular dysrhythmias

See *Chapter 22—Drugs Used to Treat Congestive Heart Failure* for a more detailed discussion of cardiac glycosides.

MAGNESIUM SULFATE

How does magnesium sulfate prevent arrhythmia?

The mechanism is not completely clear, but it is thought to stabilize cardiac cell membranes.

When do you use this drug?

For treating torsade de pointes and digoxin-induced arrhythmias

What are the adverse effects?

Bradycardia
Respiratory paralysis
Flushing
Headache

ADENOSINE (Adenocard)

How does adenosine work?

It activates acetylcholine-sensitive K^+ channels, especially in the SA and AV

nodes. This increase in K^+ conductance results in a shortening of action potential duration and hyperpolarization and decreased automaticity.

Describe adenosine's clinical role.

It is the drug of choice for treating paroxysmal supraventricular tachyarrhythmias because of limited toxicities and rapid onset.

What are the adverse effects?

Flushing
Dyspnea
Chest pain
Headache

22

Drugs Used to Treat Congestive Heart Failure

The pharmacology of most of the classes of drugs mentioned in this chapter are discussed in detail in other chapters in the book. Please note the cross-references.

Define congestive heart failure (CHF).

CHF results when cardiac output is inadequate for the metabolic demands of the body.

What are some of the most common causes of CHF?

Myocardial infarction (MI)
Hypertension (HTN)
Arrhythmia
Valvular disease
These conditions either impair the ability of cardiac muscle to contract (MI, arrhythmia) or increase the work load imposed upon the heart (HTN).

Name some of the symptoms of CHF.

Left-sided heart failure results in pulmonary edema and dyspnea. Right-sided heart failure results in liver congestion and peripheral edema.

Describe the compensatory physiologic mechanisms that occur in heart failure.

Increased sympathetic tone, which results in tachycardia
Reduced renal blood flow, which stimulates aldosterone and increases salt and water retention
Myocardial hypertrophy

Name three major pharmacologic approaches for the treatment of CHF.

1. Improve myocardial contractility
2. Reduce preload
3. Reduce afterload (the resistance against which the heart must pump)

Remember that cardiac output = heart rate \times stroke volume.

What are the pharmacologic options for treating patients who have CHF?

Cardiac glycosides
 Bipyridine derivatives
 β -adrenergic agonists
 Vasodilators
 Diuretics
 Angiotensin converting enzyme (ACE) inhibitors
 β -adrenergic blockers

CARDIAC GLYCOSIDES

Name three cardiac glycosides.

1. Digoxin (Lanoxin)
 2. Digitoxin (Crystodigin)
 3. Ouabain (no longer in use)
- Digoxin is the most widely used form because of its favorable pharmacokinetics.

Describe the mechanism of action.

Cardiac glycosides inhibit the Na^+/K^+ ATPase pump on cardiac cell membranes, which results in increased intracellular Na^+ that is then exchanged for Ca^{2+} by the $\text{Na}^+/\text{Ca}^{2+}$ exchange (Figure 22-1). The accumulation of intracellular Ca^{2+} results in increased contractility.

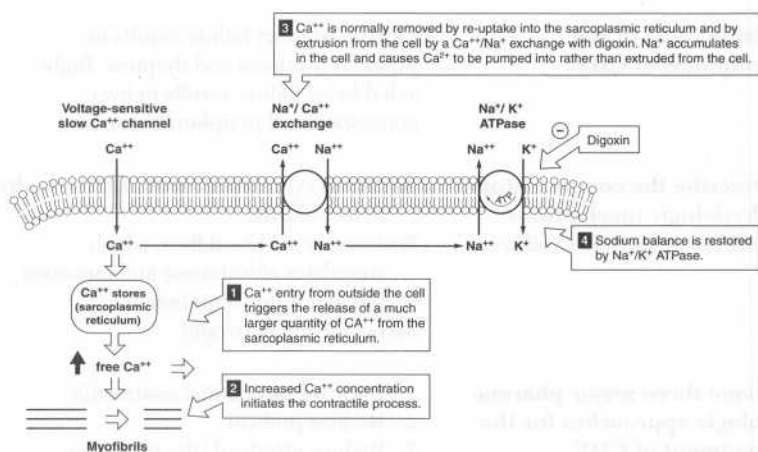


Figure 22-1. Normal ion movements during the contraction of cardiac muscle. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 154.)

How does digoxin differ from digitoxin with respect to the route of administration, half-life, % plasma bound protein, and metabolism?

	Digoxin	Digitoxin
Route of administration	PO, IV, IM	PO
Half-life	36–48 hr	4–8 days (the longer name has the longer half-life)
% plasma bound protein	20–30	90–95
Metabolism	Renal	Hepatic

Where do cardiac glycosides originate?

They are extracts of the foxglove plant, *Digitalis lanata*.

What are the clinical indications for the administration of digoxin?

Congestive heart failure
Atrial flutter and fibrillation—Digoxin slows the conduction velocity and increases the refractory period at the AV node.

State the contraindications to using these two drugs.

Bradycardia and ventricular fibrillation

What major electrolyte imbalance can predispose to digoxin toxicity?

Hypokalemia

Describe the potential ECG findings that occur with digitalis toxicity.

AV nodal block
Prolongation of the PR interval, shortening of the QT interval, and inversion of the T wave
Ventricular fibrillation
Complete heart block
Premature ventricular contraction

Patients with digoxin toxicity have what symptoms?

Nausea and vomiting
Diarrhea
Headache
Fatigue
Blurred vision
Hallucinations
Altered color perception
Rarely, gynecomastia

How do you treat digoxin toxicity?

By discontinuing use of the drug
By correcting any electrolyte imbalances

(hypokalemia can precipitate digoxin toxicity)

If necessary, by using digoxin antibodies that bind to and inactivate the drug

With a cardiac pacer if necessary

Are there any drug interactions?

Quinidine, amiodarone, and verapamil reduce plasma clearance of digoxin and can precipitate digoxin toxicity.

BIPYRIDINE DERIVATIVES

Name two bipyridine derivatives.

Amrinone (Inocor) and Milrinone (Primacor)

What is their mechanism of action?

They inhibit phosphodiesterase, which leads to increased levels of cyclic adenosine monophosphate and intracellular calcium. This subsequently results in increased contractility. Bipyridines also cause vasodilation.

Describe the route of administration.

Both of these drugs are given intravenously only.

What is their clinical role?

Bipyridines are rarely used today because of their adverse effects. In the past they were used to treat acute heart failure.

What are the major toxicities of amrinone and milrinone?

Arrhythmias
Gastrointestinal disturbances
Hepatotoxicity
Thrombocytopenia—amrinone only

β -ADRENERGIC AGONISTS

Name two β -adrenergic agonists used in the treatment of CHF.

Dobutamine (Dobutrex) and dopamine

What is their mechanism of action?

By stimulating β -adrenergic receptors, they increase cardiac contractility.

How are these drugs used clinically?

They are used to treat **acute** heart failure only; they are not indicated for chronic therapy.

See *Chapter 8—Adrenergic Agonists* for further information about β agonists.

VASODILATORS

Which vasodilators are considered appropriate for the treatment of CHF?

Nitrates (discussed in *Chapter 24—Antianginals*)
Hydralazine (Apresoline; discussed in *Chapter 20—Antihypertensive Drugs*)
ACE inhibitors

What is the reasoning behind using vasodilators?

Vasodilators reduce both preload (through venodilation) and afterload (through arterial dilation).
See *Chapter 20—Antihypertensive Drugs* for further information on vasodilators.

DIURETICS

Give some examples of diuretics.

Furosemide and hydrochlorothiazide

How do diuretics work in the treatment of congestive heart failure?

These agents reduce preload by minimizing salt and water retention. See *Chapter 23—Diuretics* for a detailed discussion of these agents.

ACE INHIBITORS

Give some examples.

Quinapril
Enalapril
Captopril
Lisinopril

Why are ACE inhibitors used in the management of CHF?

ACE inhibitors provide several benefits to patients who have heart failure:
They reduce peripheral resistance by causing vasodilation.
They minimize salt and water retention by reducing aldosterone levels.
They reduce cardiac remodeling. ("Tissue remodeling" is a term that refers to slow structural tissue changes. It includes proliferation of connective tissue cells as well as growth of abnormal myocytes.)
They have been shown to reduce mortality.
See *Chapter 20—Antihypertensive Drugs* for a detailed discussion of ACE inhibitors.

β -ADRENERGIC BLOCKERS

Name a β-adrenergic blocker approved for treatment of CHF.	Carvedilol
What is its mechanism of action?	Nonselective β -adrenergic blockade and selective α_1 -adrenergic blockade
How is it used clinically?	Although it may seem paradoxical to use β -adrenergic blockers in the treatment of CHF, recent clinical trials have shown that mortality is reduced with their use. β -adrenergic blockers seem to help by preventing the adverse effects of sympathetic output and reducing remodeling of the heart.
When should physicians employ β-adrenergic blockers?	These agents should be used only when the patient is hemodynamically stable ; they should never be used during acute heart failure.

23

Diuretics

What are diuretics?

Diuretics are drugs that increase the volume of urine flow.

How do diuretics work?

In general, diuretics affect ion transport in the nephron. Clinically useful diuretics primarily inhibit **Na⁺ reabsorption**. Water is then carried along passively in order to maintain an osmotic equilibrium.

What are their principle sites of action?

Proximal convoluted tubule (PCT)
Thick ascending limb of loop of Henle
Distal convoluted tubule (DCT)
Collecting duct
See Figure 23–1.

Why is knowing the sites of action important?

This knowledge helps predict:
The magnitude and pattern of diuresis
The side effects of the medication
The pattern of electrolyte loss

Name the five major classes of diuretics.

1. Carbonic anhydrase inhibitors
2. Loop diuretics
3. Thiazide diuretics
4. Osmotic diuretics
5. Potassium-sparing diuretics

CARBONIC ANHYDRASE INHIBITORS

What is the function of carbonic anhydrase?

Carbonic anhydrase is an enzyme that catalyzes the following reaction:



How does a carbonic anhydrase inhibitor produce diuresis?

The H^+ ion produced by the breakdown of H_2CO_3 is usually exchanged for Na^+ and is also used to combine with HCO_3^- in the lumen of the PCT. Without the H^+ there is decreased reabsorption of Na^+ and HCO_3^- ; this results in diuresis. See Figure 23–2.

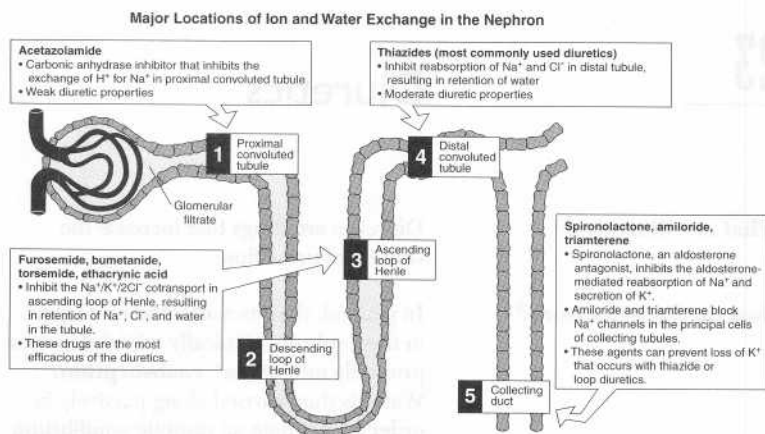


Figure 23-1. Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 224.)

How efficient is the diuresis produced by a carbonic anhydrase inhibitor?

It is relatively weak, because other sites further along in the nephron can compensate for the increased Na^+ load.

Name the prototype carbonic anhydrase inhibitor.

Acetazolamide (Diamox)

What is the route of administration?

Oral or IV

What are the clinical uses of acetazolamide?

Glaucoma—Acetazolamide decreases production of aqueous humor.
Metabolic alkalosis and acute mountain sickness—Acetazolamide inhibits carbonic anhydrase, resulting in stimulation of respiration.
Epilepsy

What are this drug's adverse effects?

Hyperchloremic metabolic acidosis caused by loss of bicarbonate
Potassium depletion caused by the sodium load and increased flow rate past the DCT
Renal calculus
Paresthesia

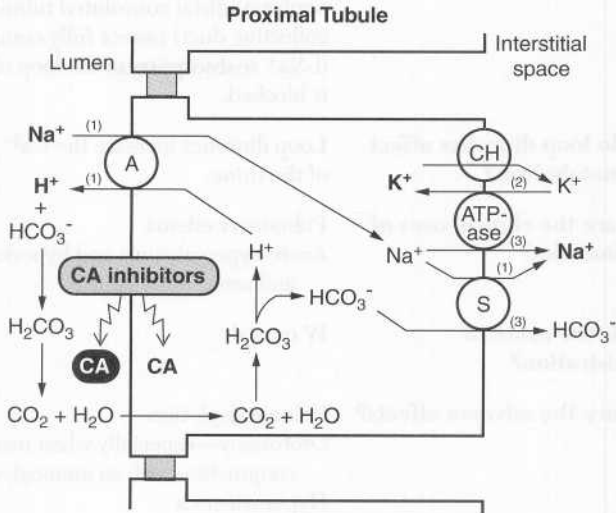


Figure 23-2. NaHCO_3 reabsorption in the proximal tubule and mechanism of diuretic action of carbonic anhydrase (CA) inhibitors. A = antiporter; S = symporter; CH = ion channel. (The actual reaction catalyzed by carbonic anhydrase is $\text{OH}^- + \text{CO}_2 \rightleftharpoons \text{HCO}_3^-$; however, $\text{H}_2\text{O} \rightleftharpoons \text{OH}^- + \text{H}^+$, and $\text{HCO}_3^- + \text{H}^+ \rightleftharpoons \text{H}_2\text{CO}_3$, so that the net reaction is $\text{H}_2\text{O} + \text{CO}_2 \rightleftharpoons \text{H}_2\text{CO}_3$.) Numbers in parentheses indicate stoichiometry. (Redrawn from Goodman and Gilman [eds]: *The Pharmacologic Basis of Therapeutics*, 7th ed. New York, Macmillan, 1985, p 693. Used with permission of The McGraw-Hill Companies.)

Drowsiness

Interstitial nephritis—Acetazolamide is a sulfonamide derivative.

LOOP DIURETICS

Name the loop diuretics.

Furosemide (Lasix), ethacrynic acid (Edecrin), and bumetanide (Bumex)

What are the mechanism of action and site of action of these drugs?

Loop diuretics work by blocking the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ co-transport system in the **thick ascending limb of the loop of Henle**.

Why are the loop diuretics also called “high ceiling diuretics”?

Because they have the highest efficacy of all diuretics

Why are they the most efficacious diuretics?

25% to 35% of NaCl is normally reabsorbed at the ascending loop of Henle. Sites downstream along the

nephron (distal convoluted tubule and collecting duct) cannot fully compensate if Na^+ reabsorption in the loop of Henle is blocked.

How do loop diuretics affect Ca^{2+} metabolism?	Loop diuretics increase the Ca^{2+} content of the urine.
What are the clinical uses of loop diuretics?	Pulmonary edema Acute hypercalcemia and hyperkalemia, and acute renal failure
What is the route of administration?	IV or oral
What are the adverse effects?	Volume depletion Ototoxicity—especially when used in conjunction with an aminoglycoside Hyperuricemia Hypokalemia Hypomagnesemia Hypocalcemia Hyperchloremic metabolic alkalosis Interstitial nephritis—Loop diuretics are sulfonamide derivatives.

THIAZIDE DIURETICS

What are they?	Sulfonamide derivatives related structurally to the carbonic anhydrase inhibitors
Give some examples.	Chlorothiazide-prototype Hydrochlorothiazide (HydroDIURIL) Metolazone and Indapamide-thiazide analogues
Where do they work?	All thiazides work in the early segment of the distal convoluted tubule.
How do they work?	They block Na^+/Cl^- co-transport on the luminal side of the distal convoluted tubule.
How effective are thiazides?	They are only moderately effective because most of the filtered Na^+ is absorbed before it reaches the DCT.
What are the uses of thiazides?	They are used to treat: Hypertension

Congestive heart failure

Nephrosis

Hypercalciuria

Nephrogenic diabetes insipidus—

Thiazides have the ability to produce a hyperosmolar urine and thus diminish polyuria.

Which thiazides are most effective?

All thiazides are equally effective; they differ only in potency.

How do thiazides affect Ca^{2+} levels?

Thiazides, unlike loop diuretics, **increase** Ca^{2+} levels in the blood, so watch for hypercalcemia.

What are the side effects of thiazide diuretics?

Hypokalemia

Hypochloremic metabolic alkalosis

Hyperuricemia

Hyperglycemia

Hyperlipidemia

Hyponatremia

Hypercalcemia

OSMOTIC DIURETICS

What are the most commonly used osmotic diuretics?

Mannitol and urea

What is their mechanism of action?

Osmotic diuretics are freely filterable substances; once they become a component of the luminal fluid, they create an osmotic effect along the entire nephron, but especially at the PCT and collecting duct.

What are the clinical uses of these drugs?

Osmotic diuretics are mainly used in a hospital setting to treat increased intracranial and intraocular pressure and acute renal failure.

What is the route of administration?

These drugs must be given IV; other modes of administration will cause cathartic diarrhea.

What are the toxicities associated with osmotic diuretics?

Hypovolemia

Hypernatremia

Can cause pulmonary edema because they rapidly enter the extracellular compartment and pull water out of cells

POTASSIUM-SPARING DIURETICS

Give examples of this class of drugs.

Spironolactone (Aldactone)
Amiloride (Midamor)
Triamterene (Dyrenium)

What is their mechanism of action?

They work primarily by inhibiting the passage of sodium in the luminal fluid into the principal cells of the late distal convoluted tubule and cortical collecting tubule. Subsequently, this prevents the movement of K^+ from these cells into the luminal fluid. See Figure 23-3.

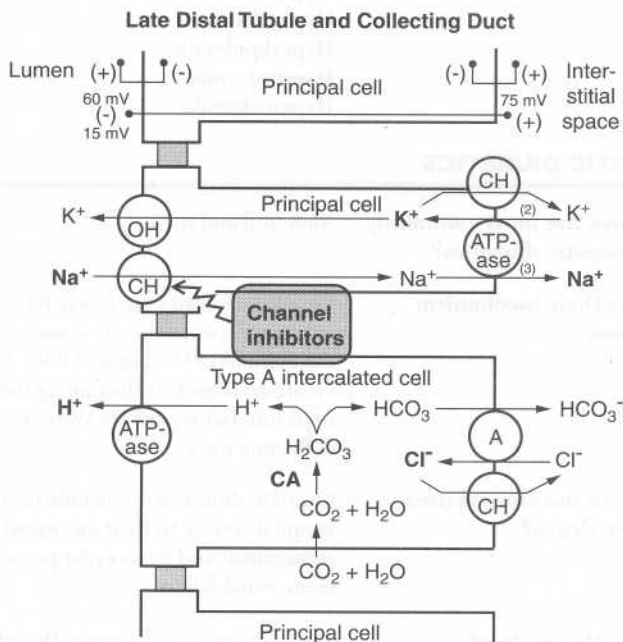


Figure 23-3. Na^+ reabsorption in the late distal tubule and collecting duct and mechanism of diuretic action of Na^+ channel inhibitors. Cl^- reabsorption (not shown) occurs both paracellularly and transcellularly, and the precise mechanism of Cl^- transport appears to be species-specific. A = antiporter; CH = ion channel; CA = carbonic anhydrase. Numbers in parentheses indicate stoichiometry. Designated voltages are the potential differences across the indicated membrane or cell. (Redrawn from Goodman and Gilman [eds]: *The Pharmacologic Basis of Therapeutics*, 7th ed, p 703. New York, Macmillan, 1985. Used with permission of The McGraw-Hill Companies.)

What is the efficacy of these drugs?

Weak. They are used today primarily in conjunction with another diuretic such as a thiazide in order to limit K^+ wasting.

What is spironolactone?

This drug is a synthetic steroid that is a competitive antagonist for the mineralocorticoid aldosterone. It binds to aldosterone receptor sites and prevents the formation of mediator proteins that stimulate the Na^+/K^+ pump.

What are the clinical indications for the use of spironolactone?

Primary hyperaldosteronism (Conn's syndrome)

Edematous states caused by secondary aldosteronism, especially cirrhosis, nephrotic syndrome, and cardiac failure

Are there problems associated with administration of spironolactone?

Gynecomastia and impotence, owing to spironolactone's structural similarity to progesterone

How does spironolactone differ from triamterene and amiloride?

Amiloride and triamterene work independently of aldosterone by directly blocking the Na^+ channels; therefore, these agents can be used even in cases of hypoaldosteronism such as Addison's disease. In contrast, spironolactone requires elevated levels of aldosterone to have an effect.

What are the adverse effects of potassium-sparing drugs?

Hyperkalemia—most important effect to watch for

Metabolic acidosis—because of an intracellular shift of H^+ ions

Rarely, triamterene forms renal stones.

24

Antianginal Drugs

What is the definition of angina pectoris?

Sudden substernal chest pain caused by coronary blood flow that is insufficient to meet the oxygen demands of the myocardium

Identify the three types of angina.

1. Classic (stable) angina—chest pain occurring upon **exertion** that is usually due to an atheromatous lesion
2. Unstable angina—angina that suddenly becomes worse or that occurs at rest
3. Prinzmetal's (variant) angina—a form of angina that results from coronary vasospasm

Which type accounts for most angina cases?

Classic angina accounts for approximately 90% of cases.

What percentage of patients who have unstable angina progress to an MI?

10%–20%

What is the treatment strategy for angina?

Because angina is caused by O_2 demand greater than O_2 supply (Figure 24–1), there are two treatment options:

1. Increase oxygen delivery.
2. Decrease cardiac oxygen demand.

What is myocardial oxygen demand dependent upon?

Preload—diastolic filling pressure
Afterload—peripheral vascular resistance
Heart rate
Wall tension

Name four major classes of drugs used to treat angina.

1. Nitrates
2. Calcium channel blockers
3. β -blockers
4. Aspirin

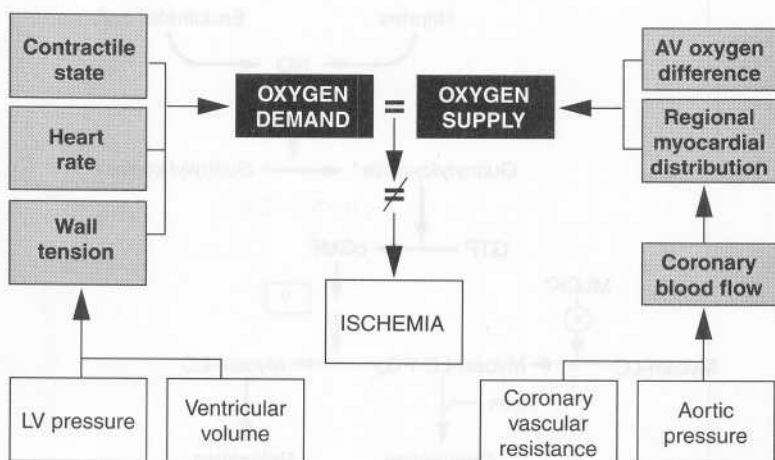


Figure 24-1. Ischemic episodes: an imbalance in the myocardial oxygen supply-demand relationship. (Redrawn from Ross RS: Pathophysiology of coronary circulation. *Br Heart J* 33:173—184, 1971.)

Why is aspirin useful in treating angina?

Because of its ability to inhibit platelet aggregation, aspirin has been shown to reduce mortality in patients who have unstable angina. (Aspirin is discussed further in *Chapter 35—Anti-inflammatory Drugs and Acetaminophen*.)

NITRATES

How do nitrates relieve angina?

Nitrates relax vascular smooth muscle through conversion into nitric oxide (NO) and subsequent elevation of intracellular cyclic guanosine monophosphate (cGMP) levels. The increased activity of cGMP ultimately leads to dephosphorylation of myosin light chains and smooth muscle relaxation (Figure 24-2).

What is the principle physiologic effect of low doses of nitroglycerin?

Dilation of the veins, which causes a diminished preload and reduced cardiac output

What happens at higher doses of nitrates?

Arterioles become dilated, which leads to a decrease in peripheral resistance and blood pressure.

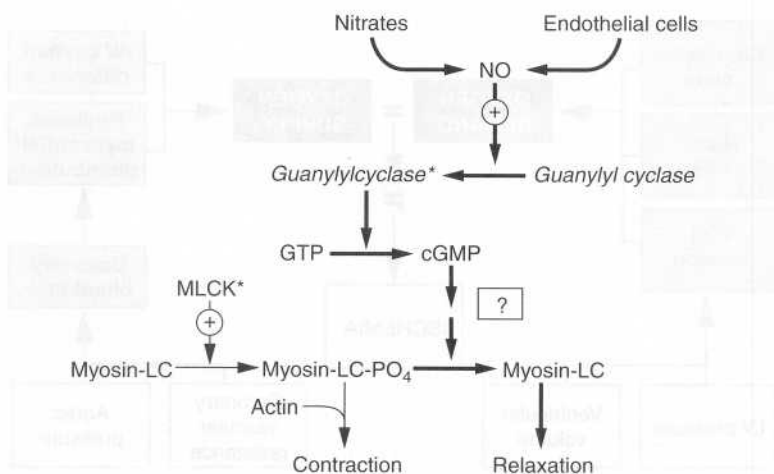


Figure 24–2. Mechanism of action of nitrates, nitrites, and other substances that increase the concentration of nitric oxide (NO) in smooth muscle cells. *MLCK** = activated myosin light chain kinase; *guanylyl cyclase** = activated guanylyl cyclase; ? = unknown intermediate steps. Steps leading to relaxation are shown with heavy arrows. (Redrawn from Katzung BG: *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT, Appleton & Lange, 1998, p 181.)

Give three examples of nitrates and their routes of administration.

1. Nitroglycerin—sublingual (Nitrostat), transdermal (Nitro-Dur), oral (Nitro-Bid), and IV
2. Isosorbide dinitrate—oral
3. Amyl nitrate—inhaled

What are the pharmacokinetics of nitroglycerin?

An extensive first-pass metabolism of nitroglycerin (90%) occurs in the liver. Therefore, it is common to give the drug sublingually or through the use of a transdermal patch.

What are the therapeutic uses of nitroglycerin?

Acute anginal attacks—Use the sublingual form of nitroglycerin because the onset of action is seconds to minutes.

Prevention of attacks—Use the oral or transdermal form of nitroglycerin.

Does tolerance develop to nitrates?

Yes—therefore, it is important to have nitrate-free periods during long-term use.

What are the toxicities of nitrates due to vasodilation?

Postural hypotension
Dizziness
Reflex tachycardia

Throbbing headaches due to meningeal artery dilation
Hot flushes

Name two important uses for nitrates other than angina.

1. Nitroglycerine in combination with hydralazine has been shown to decrease mortality in patients who have heart failure.
2. They are used in the treatment of cyanide poisoning (see *Chapter 51—Toxicology*).

CALCIUM CHANNEL BLOCKERS

Give three examples of this drug class.

1. Nifedipine (Procardia)
2. Verapamil (Calan)
3. Diltiazem (Cardizem)

What is the mechanism of action?

All three drugs inhibit the influx of Ca^{2+} into cardiac and smooth muscle cells by blocking voltage-dependent “L-type” calcium channels, thereby reducing smooth muscle and cardiac contractility. The degree of blockade is proportional to the degree of stimulation of these calcium channels.

What are the therapeutic uses?

Calcium channel blockers are the drugs of choice for Prinzmetal’s angina. They can also be used for chronic stable angina, migraine, hypertension, supraventricular arrhythmias, and Raynaud’s syndrome.

What are the special traits of verapamil?

Of the three calcium channel blockers, verapamil has the most inhibitory effect on cardiac conduction, especially at the atrioventricular (AV) node. It also tends to increase digoxin levels.
(Remember **V** for Ventricle.)



What is the site of action for nifedipine?

It mainly acts on arterioles and therefore causes the greatest decrease in blood pressure. Unlike verapamil, it has little effect on cardiac conduction or heart rate.

What are the special traits of diltiazem?

Diltiazem is an intermediate drug when compared to verapamil and nifedipine. It has moderate effects on cardiac conduction and blood pressure.

How can Ca^{2+} channel blockers be administered? IV, PO, or sublingual

List the possible toxic effects of the calcium channel blockers. Headache
Dizziness
Nausea
Constipation

More serious complications:

Congestive heart failure
AV node blockage

β BLOCKERS

See Chapter 9—*Adrenergic Antagonists* for a detailed discussion of β blockers.

What is the role of β blockers in angina? They help reduce the frequency and severity of classic (but not variant) anginal attacks by decreasing: (1) heart rate, (2) contractility, and (3) blood pressure, thus reducing myocardial oxygen demand.

What are the contraindications to the use of these drugs? Patients who have asthma, diabetes, and peripheral vascular disease should be given β blockers only with extreme caution. Use Ca^{2+} channel blockers as an alternative.

How do you decide which β blocker to use? All can be effective, but atenolol, timolol, and metoprolol are three of the most commonly used because they are cardioselective.

Can these drugs be used in combination? Yes. Because the different categories of agents work with different mechanisms of action, they can be used together to produce added benefits.

25

Anticoagulant, Fibrinolytic, and Antiplatelet Drugs

Define the term *thrombus*.

A thrombus is a clot that forms within a vessel and that can completely occlude the vessel.

What causes a thrombus?

A pathologic condition of the vascular system such as endothelial damage or vascular stasis that initiates a complex series of interactions between platelets, endothelial cells, and the coagulation cascade (Figure 25-1). In contrast, a simple blood clot involves only the coagulation sequence.

What are the two major pathways of coagulation cascade, and what activates each?

1. The **extrinsic system** is initiated by the release of tissue thromboplastin and the activation of clotting factor VII.
2. The **intrinsic system** is initiated by the activation of clotting factor XII.

Name two drugs commonly used to anticoagulate a patient.

1. Heparin
2. Coumadin

HEPARIN

What type of chemical compound is heparin?

Heparin is a highly acidic straight-chain glycosaminoglycan.

Does heparin exist normally within the body?

Yes, heparin is normally found in a complex with histamine in mast cells. Its physiologic role has yet to be completely elucidated.

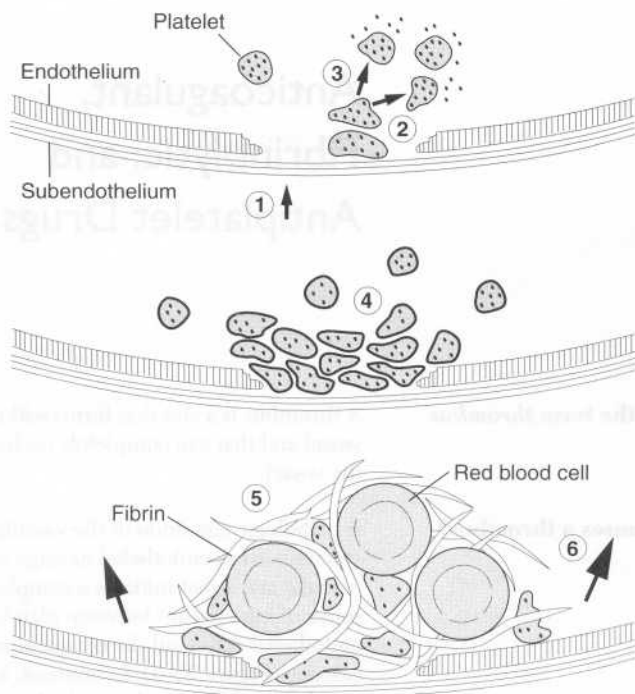


Figure 25-1. Summary of thrombogenesis. ① Endothelial injury releases tissue factor and exposes subendothelial connective tissues. ② Platelet adherence and plasma clotting system are triggered. ③ Granule release and prostaglandin generation begin. ④ Platelet aggregation induced by released ADP and vasoconstriction (5HT, thromboxanes) result in primary (temporary) hemostatic plug. ⑤ Thrombin, thromboxanes, and endoperoxides promote release reaction and irreversible aggregation; amorphous platelet mass and trapped red cells are enmeshed in fibrin to form definitive (permanent) hemostatic plug. ⑥ Endothelial plasminogen activator and plasma antithrombin check rapid clotting. (Time scale: Steps 1—4 = seconds to minutes; steps 5—6 = several minutes.) Adapted from Cotran RS, Jumar V, Robbins SL: *Robbins Pathologic Basis of Disease*, 5th ed. Philadelphia: WB Saunders, 1994.

How does heparin work?

Antithrombin III is a naturally occurring α_2 -globulin that binds to and inactivates clotting factors IIa, IXa, Xa, XIa, and XIIa. This process is normally very slow; heparin binds to antithrombin III and accelerates the reaction a thousandfold.

What is heparin's major indication?

Because of its rapid onset of action, heparin is used whenever immediate initiation of anticoagulation is needed, for example, in treating pulmonary embolism and deep vein thrombosis.

What other uses does heparin have?	Heparin can also be used prophylactically to prevent postoperative embolisms.
What are the limitations of heparin?	Heparin stops the expansion of thrombi and prevents the formation of new thrombi. However, it does not dissolve existing thrombi.
What is the route of administration?	Heparin must be given either subcutaneously or intravenously. Intramuscular injections must be avoided because of potential hematoma formation.
What measure is used to monitor the actions of heparin—prothrombin time (PT) or activated partial thromboplastin time (aPTT)?	aPTT
How is this drug metabolized?	By the liver
Is heparin safe to use in pregnant women?	Yes—with qualifications. The drug will not cross the placenta. Heparin is probably the preferred anticoagulant for pregnant women, but it is <i>not risk free</i> . Approximately 13% to 20% of pregnant women who use this drug experience outcomes such as stillbirths and prematurity. Therefore, <i>use heparin cautiously</i> , especially during the last trimester.
What adverse effects should you watch for when administering heparin?	<p>Hemorrhage—most important effect to watch for</p> <p>Hypersensitivity reaction—watch for chills, fever, or urticaria</p> <p>Thrombocytopenia—After approximately a week of heparin administration, patients may develop heparin-induced antiplatelet antibodies.</p> <p>Alopecia and osteoporosis—associated with long-term use</p>
How do you counteract the effects of heparin?	Use protamine sulfate (a common board question)
What are the contraindications to the administration of heparin?	<p>Patients who have had any of the following should avoid using heparin:</p> <p>A hypersensitivity reaction</p>

A bleeding disorder
Surgery of the brain, eye, or spinal cord
Intracranial hemorrhage
Infective endocarditis

WARFARIN (COUMADIN)

How is warfarin different from heparin?

Warfarin is administered orally, has a delayed onset of action, and crosses the placenta.

What is warfarin's mechanism of action?

Warfarin interferes with the synthesis of vitamin K, which is needed for γ -carboxylation of factors II, VII, IX, and X as well as coagulation factors protein C and S.

Describe warfarin's onset of action.

Compared with heparin, warfarin has a delayed onset of action (usually 8–12 hours) that relates to the half-life of preformed vitamin K-dependent clotting factors.

When would you use this drug?

When long-term anticoagulation is needed, such as for patients with atrial fibrillation, for prevention of stroke, and for patients with a mechanical heart valve

How do you monitor the effects of warfarin?

Use the INR (international normalized ratio).

Can you use this drug in pregnant women?

No! The drug has teratogenic effects.

How is warfarin metabolized?

It is metabolized in the liver; after conjugation to glucuronic acid, warfarin is excreted in the stool.

What drugs potentiate the actions of warfarin?

Alcohol
Cimetidine (Tagamet)
Disulfiram
Phenylbutazone

What is the principal toxicity of warfarin?

Hemorrhage

How do you reverse the actions of warfarin?

Administer vitamin K or fresh frozen plasma, and allow 24 hours for full reversal.

FIBRINOLYTICS

Give three examples of fibrinolytics.

1. Streptokinase (Streptase)
2. Urokinase (Abbokinase)
3. Tissue plasminogen activator (alteplase)

What is the function of the fibrinolytic system?

It provides a mechanism for the degradation of fibrin clots.

What is the role of plasmin in the fibrinolytic system?

Plasmin is a serine protease that hydrolyzes fibrin into fibrin split products and therefore dissolves clots. Plasminogen is the precursor of plasmin (Figure 25-2).

Do fibrinolytics distinguish between beneficial hemostatic plugs and unwanted thrombi?

No—This is a disadvantage of the fibrinolytics. Newer drugs are more selective with more limited systemic bleeding.

How are all fibrinolytics administered?

IV

STREPTOKINASE

Where does streptokinase come from?

Streptokinase is an extracellular protein derived from purified culture broth of group C β -hemolytic streptococci.

When do you use it?

Streptokinase is used in cases where rapid clot dissolution is needed, such as acute pulmonary embolism, deep vein thrombosis, acute myocardial infarction, and arterial thrombosis.

How does streptokinase work?

Streptokinase itself has no enzymatic ability; it must first bind plasminogen. The streptokinase-plasminogen complex then converts uncomplexed plasminogen into plasmin.

What are the toxicities of streptokinase?

Systemic bleeding
Drug allergy, which may result in rashes or fever

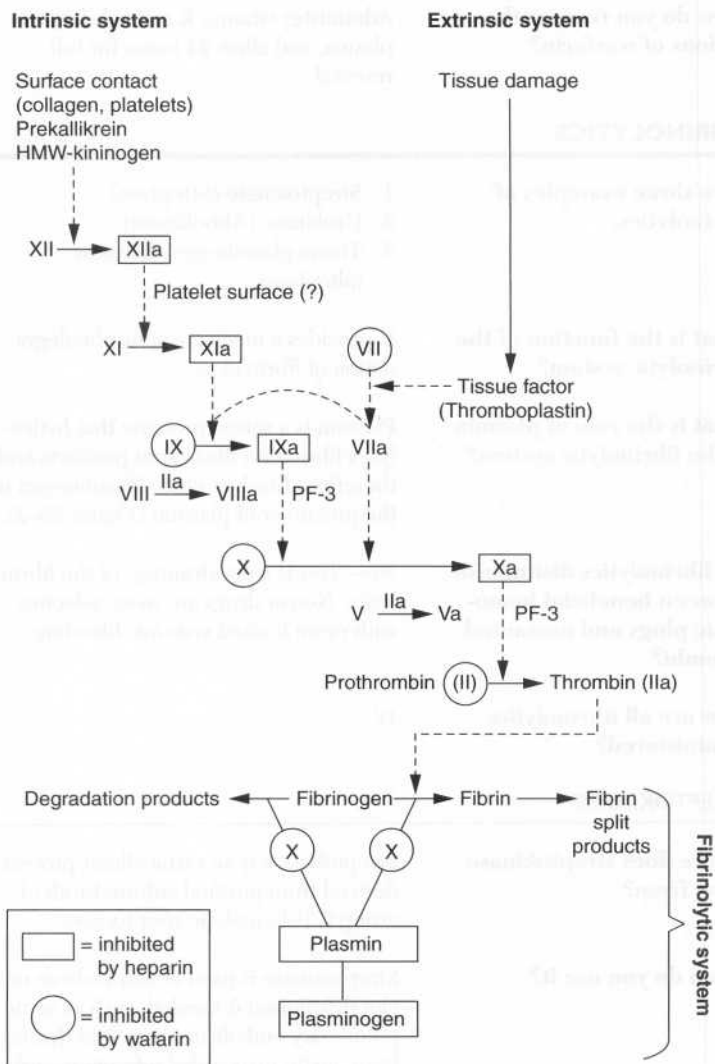


Figure 25-2. The intrinsic pathway is initiated when blood comes in contact with the negatively charged de-endothelialized vascular surface. Factor XII is activated, and, in a sequential reaction, factors XI and IX are activated. On the platelet surface, factors IXa and VIII interact with calcium and activate factor Xa. In the extrinsic pathway, tissue thromboplastin is released after vessel wall injury activates factor VII, which in turn activates factor X. Then, on the platelet surface, factors Xa and Va interact with calcium and catalyze the conversion of prothrombin to thrombin. Thrombin converts fibrinogen to fibrin monomers and activates factor XIII, which in turn is converted to fibrin polymers in the developing clot. Note that factor VII from the extrinsic pathway may activate factor IX in the intrinsic pathway. (Adapted and redrawn from Cotran RS, Jumar V, Robbins SL: *Robbins Pathologic Basis of Disease*, 5th ed. Philadelphia, WB Saunders, 1994.)

UROKINASE (Abbokinase)

How does urokinase work?

Unlike streptokinase, which must first bind with plasminogen, urokinase is capable of directly degrading both fibrin and fibrinogen.

What are its therapeutic use?

Urokinase is effective in treating pulmonary embolism and deep vein thrombosis.

What are the adverse effects?

Bleeding complications

TISSUE PLASMINOGEN ACTIVATOR (Alteplase)

Classify tissue plasminogen activator (TPA).

It is a serine protease that is obtained through recombinant DNA technology.

What is the major advantage of TPA over other thrombolytics?

In theory, it binds to plasminogen bound to fibrin rather than free plasminogen, thus decreasing the risk of systemic bleeding.

What are the indications for this agent?

TPA is only used for the treatment of acute myocardial infarction.

State its adverse effects.

Bleeding complications, especially cerebral hemorrhage, are the most important adverse effects to watch for.

How do you reverse the actions of streptokinase, urokinase, and TPA?

Use aminocaproic acid (Amicar). It binds to plasmin and plasminogen, and thus prevents plasmin from binding to fibrin.

ANTIPLATELET DRUGS

What is the action of the antiplatelet drugs?

They delay clot formation by inhibiting platelet aggregation. This delay ("bleeding time") can be measured by the lab.

ASPIRIN

See *Chapter 35—Anti-inflammatory Drugs and Acetaminophen* for more detailed information on aspirin.

What is aspirin's mechanism of action?

Aspirin *irreversibly* inhibits platelet aggregation and inhibits thromboxane A_2 synthesis by blocking the enzyme cyclooxygenase.

What is aspirin's role in anticoagulating a patient?

One aspirin a day has been shown to be beneficial in preventing clot formation. It is not helpful in acute situations such as a sudden pulmonary embolism.

State aspirin's adverse effects.

Nausea
Gastrointestinal bleeding
Rash
Reversible hepatic dysfunction

TICLOPIDINE (Ticlid)

Describe the mechanism of action.

Ticlopidine interferes with platelet function by inhibiting adenosine diphosphate-induced binding of fibrinogen to the platelet membrane.

What are its uses?

Ticlopidine reduces the risk of thrombotic stroke. Because ticlopidine is associated with the risk of neutropenia and agranulocytosis, reserve its use for patients who cannot take aspirin.

What are the adverse effects of this drug?

Gastrointestinal complaints (diarrhea, nausea)
Skin rash
Bleeding complications
Neutropenia
Agranulocytosis

DIPYRIDAMOLE (Persantine)

What is dipyridamole's mechanism of action?

The mechanism of action is uncertain, but dipyridamole is thought to interfere with platelet function by increasing cyclic adenosine monophosphate (cAMP), either by blocking uptake of adenosine or by inhibiting phosphodiesterase.

What are its uses?

Dipyridamole is used to prevent thrombosis in patients who have artificial heart valves. It is also used to image regions of myocardium at risk for ischemia (Persantine-thallium scans).

What are dipyridamole's adverse effects?

Dizziness
Angina
Abdominal pain
Headache
Rash

SULFINPYRAZONE (Anturane)

What is sulfinpyrazone's mechanism of action?

Sulfinpyrazone inhibits platelet granule release and prostaglandin synthesis, which prevents platelet aggregation.

What are its uses?

Sulfinpyrazone decreases the frequency of systemic embolism in patients who have rheumatic mitral stenosis.

State the adverse effects.

Upper gastrointestinal disturbances
Rash
Blood dyscrasias—*anemia, leukopenia, aplastic anemia*
Renal calculi
Acute gouty arthritis

Antihyperlipidemic Drugs

Coronary heart disease (CHD) is one of the most common causes of death in the United States. Almost half of the deaths annually from CHD are associated with hyperlipidemia.

What is treatment of CHD based upon?

According to the National Cholesterol Education Program Guidelines, the decision to treat is based on low-density lipoprotein (LDL) levels. Drug therapy should be initiated at LDL levels ≥ 190 mg/dL in a patient who does not have CHD or who has two or fewer risk factors for CHD.

What is a lipoprotein?

A macromolecule made of protein which carries lipids

Name the major lipoproteins.

Chylomicrons
High-density lipoproteins (HDLs)
Low-density lipoproteins (LDLs)
Intermediate-density lipoproteins (IDLs)
Very-low-density lipoproteins (VLDLs)
Figure 26-1 illustrates their physiologic roles.

What causes hyperlipidemias?

Hyperlipidemias can be organized into two categories, primary and secondary, based on their causes:

1. **Primary hyperlipidemias** are caused by genetic defects and/or environmental factors. Table 26-1
2. **Secondary hyperlipidemias** are a result of other metabolic disorders such as diabetes, hypothyroidism, renal disease, and alcoholism.

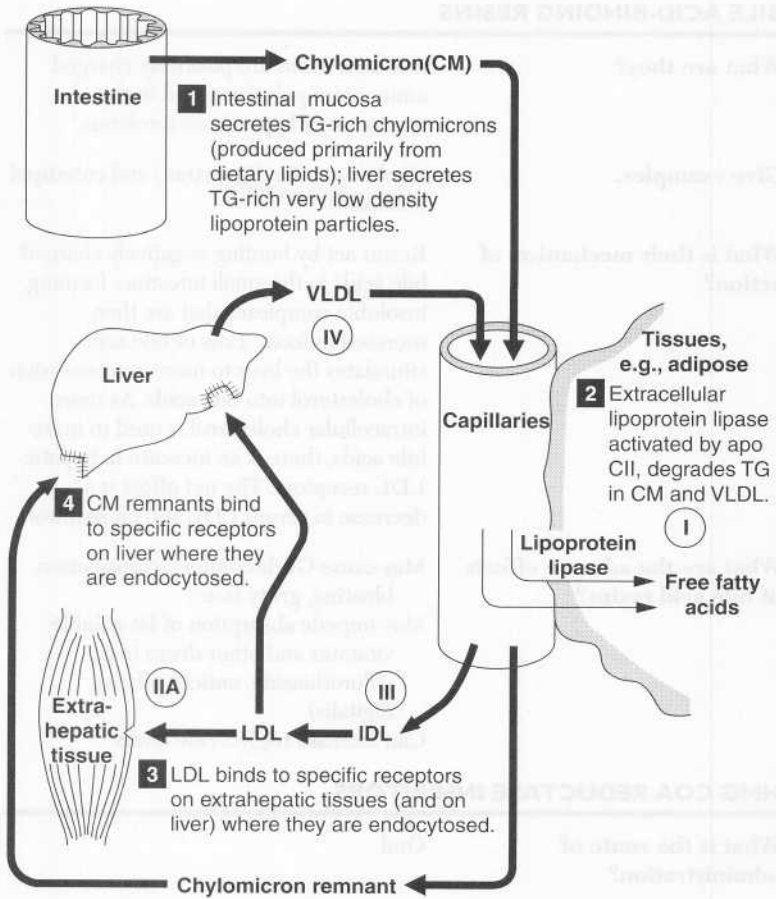


Figure 26-1. Metabolism of plasma lipoproteins and related genetic diseases. CM = chylomicron; TG = triacylglycerol; VLDL = very low density lipoprotein; LDL = low density lipoprotein; IDL = intermediate density lipoprotein; apo CII = apoprotein CII found in chylomicrons and VLDL. The Roman numerals in the white circles refer to specific genetic types of hyperlipidemias. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 200.)

What are the treatment options?

Diet and exercise management—always the first intervention

- Bile acid-binding resins
- HMG CoA reductase inhibitors
- Fibric acid derivatives
- Niacin

BILE ACID-BINDING RESINS

What are they?

Bile acid resins are positively charged ammonium polymers used in the treatment of hypercholesterolemia.

Give examples.

Cholestyramine (Questran) and colestipol (Colestid)

What is their mechanism of action?

Resins act by binding negatively charged bile acids in the small intestine, forming insoluble complexes that are then excreted in feces. Loss of bile acids stimulates the liver to increase conversion of cholesterol into bile acids. As more intracellular cholesterol is used to make bile acids, there is an increase in hepatic LDL receptors. The net effect is a decrease in serum LDL and cholesterol.

What are the adverse effects of bile acid resins?

May cause GI discomfort (constipation, bloating, gritty taste)
May impede absorption of fat-soluble vitamins and other drugs (e.g., chlorothiazide, anticoagulants, digitalis)
Can increase triglyceride levels

HMG COA REDUCTASE INHIBITORS

What is the route of administration?

Oral

Give examples of these drugs.

Lovastatin (Mevacor)
Simvastatin (Zocor)
Pravastatin (Pravachol)
Fluvastatin (Lescol)
Atorvastatin (Lipitor)
Remember to look for the suffix
“-statin.”



What is HMG CoA reductase?

The rate-determining enzyme in the synthesis of cholesterol, which converts HMG CoA to mevalonic acid (Figure 26-2)

What is the role of reductase inhibitors on hyperlipidemia?

HMG CoA reductase inhibitors decrease cholesterol synthesis in the liver, which leads to an increase in hepatocyte surface LDL receptors.

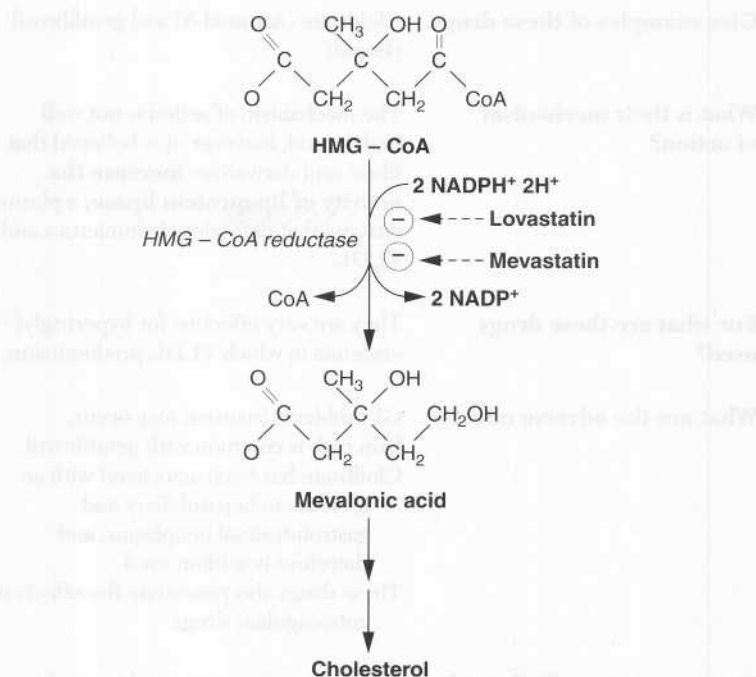


Figure 26-2. Inhibition of HMG-CoA reductase by lovastatin and mevastatin. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 205.)

What are the adverse effects? Increase in hepatic transaminase levels
Myopathy

What other drugs should generally not be prescribed to a patient taking HMG CoA reductase inhibitors? Fibrin acid derivatives
Cyclosporine
Niacin
Erythromycin
The incidence of myopathy associated with rhabdomyolysis increases when a reductase inhibitor is used with these drugs.

FIBRIC ACID DERIVATIVES

What are they? Fibrin acid derivatives are ethyl esters that cause catabolism of VLDLs and chylomicrons.

By what route are they administered? Oral

- Give examples of these drugs.** Clofibrate (Atromid-S) and gemfibrozil (Lopid)
- What is their mechanism of action?** The mechanism of action is not well understood; however, it is believed that fibric acid derivatives **increase the activity of lipoprotein lipase**, a plasma enzyme that degrades chylomicrons and VLDL.
- For what are these drugs used?** They are very effective for hypertriglyceridemia in which VLDL predominates.
- What are the adverse effects?** GI problems (nausea) may occur. Skin rash is common with gemfibrozil. Clofibrate has been associated with an increase in hepatobiliary and gastrointestinal neoplasms, and therefore is seldom used. These drugs also potentiate the effects of anticoagulant drugs.
- Can you ever use fibric acid derivatives with HMG CoA reductase inhibitors for added benefits?** When these drugs are used in combination, the risk of rhabdomyolysis usually outweighs the benefits.
- Are these drugs safe to use in pregnancy?** No

NIACIN (NICOTINIC ACID)

- What is it?** Pyridine-3-carboxylic acid, a part of the vitamin B complex (formerly known as vitamin B₃). Niacin is different from nicotinamide, which has no efficacy in the treatment of hypercholesterolemia.
- What is niacin's clinical use?** Treatment of elevated LDL and/or elevated triglycerides, with or without decreased HDL.
- What are niacin's mechanisms of action?** Decreases adipose tissue lipolysis, which in turn reduces circulating free fatty acids and hepatic triacylglycerol synthesis

Table 26–1. Pharmacologic Management of Lipid Disorders

Laboratory Findings	Type	Cause	Drug Therapy
↑ chylomicrons	I Familial hyperchylomicronemia	Deficiency of lipoprotein lipase or deficiency of apoprotein CII	Gemfibrozil to prevent pancreatitis if chylomicrons > 400 mg/dL
↑ LDL	IIa Familial hypercholesterolemia	Absence of or defective LDL receptors	HMG CoA reductase inhibitor, niacin, resin
↑ LDL ↑ VLDL ↓ HDL	IIb Familial combined hyperlipidemia	↑ secretion of VLDL (biochemical cause unknown)	Niacin, HMG CoA reductase inhibitor, gemfibrozil, resin
↑ IDL ↑ chylomicrons ↓ LDL ↓ HDL	III Familial dysbetalipoproteinemia	↑ production or ↓ utilization of IDL (defect in ApoEII)	Niacin, gemfibrozil
↑ VLDL ↓ HDL	IV Familial hypertriglyceridemia	↑ secretion of VLDL (biochemical cause unknown)	Niacin, bile acid resins
↑ VLDL ↑ chylomicrons	V Familial mixed hypertriglyceridemia	↑ production or ↓ removal of VLDL and chylomicrons (biochemical cause unknown)	Drug therapy if necessary

(Adapted from Gallia G, Hann CL, Hewson WH: *The Pharmacology Companion*. La Jolla, CA, Alert & Oriented Publishing Company, 1997, p 145.)

Increases the activity of lipoprotein lipase
Causes a reduction of VLDL from the liver
Stimulates mild-to-moderate increases in HDL

What are its adverse effects?

A cutaneous flush accompanied by pruritus is one of the most common problems; aspirin can alleviate this problem.
Liver toxicity—This must be monitored by liver function tests at least every 6 months.
Hyperglycemia
Hyperuricemia
Nausea
Constipation

How do you treat acute iron intoxication?

Immediate treatment is necessary and usually consists of removal of unabsorbed tablets from the gut as well as administration of a chelating agent known as deferoxamine.

How do you manage chronic iron intoxication?

Treatment consists of regular phlebotomy.

CYANOCOBALAMIN (VITAMIN B₁₂)

What is the function of vitamin B₁₂?

Vitamin B₁₂ is a cofactor in the transfer of one-carbon units, which is a step necessary in the synthesis of DNA.

What is necessary for the absorption of vitamin B₁₂?

Presence of intrinsic factor, which is produced by the parietal cells of the stomach

Is vitamin B₁₂ stored within the body?

Yes! Vitamin B₁₂ is stored in the liver. The average person has a 5-year supply.

What are the three most common causes of B₁₂ deficiency?

1. Pernicious anemia
2. Total gastrectomy
3. Disorders of the distal ileum

What symptoms are caused by vitamin B₁₂ deficiency?

Vitamin B₁₂ deficiency causes megaloblastic anemia and tabes dorsalis, which is a neurologic disease characterized by degeneration of the posterior spinal columns.

What is its therapeutic use?

Vitamin B₁₂ is used for the treatment of naturally occurring pernicious anemia and anemia caused by gastric resection.

What is the route of administration?

Parenteral injections, because vitamin B₁₂ deficiency is most commonly caused by poor absorption

What is its toxicity?

There are no known adverse effects!

FOLIC ACID

What is the physiologic function of folic acid?

Folic acid is necessary for the transfer of one-carbon fragments in the synthesis of purine and pyrimidine bases.

Agents Used to Treat Anemia

Define anemia.

A red blood cell count, hemoglobin or hematocrit concentration that is below normal plasma levels. Conditions that increase plasma volumes, such as pregnancy, will cause a relative anemia, not a true anemia.

Name the major categories of anemia.

Microcytic anemia
Normocytic anemia
Macrocytic or megaloblastic anemia

IRON

What type of anemia is caused by iron deficiency?

A hypochromic microcytic anemia

What are the two major causes of iron deficiency?

1. GI bleeding
 2. In women, menstrual blood loss
- Iron deficiency can also be caused by pregnancy and by periods of rapid growth in children.

How is iron distributed in the body?

Most of the iron present within the body is in hemoglobin. Iron is also bound to transferrin (a transport protein) and stored as ferritin and hemosiderin.

What are the reasons for administering iron?

Iron deficiency anemia is the only indication for the use of iron.

What form of iron is administered?

Iron is most commonly given by oral ferrous iron supplementation.

What are the toxicities of iron?

Gastrointestinal disturbance (necrotizing gastroenteritis) is the most common symptom. If the dose is sufficiently high, shock, metabolic acidosis, and even death can occur.

What are its clinical indications?

Folic acid is used in the treatment of megaloblastic anemia. It is important to rule out vitamin B₁₂ deficiency before administering folic acid as sole therapy because folic acid will not remedy the neurologic deficits.

Other than for treating anemia, when is folic acid important?

Folic acid is critical during pregnancy. Without it there is a markedly increased risk of neural tube defects.

Is folate stored in the body as much as vitamin B₁₂ is?

No! Folate supply will run out in just 3 months, whereas vitamin B₁₂ supplies last for 5 years!

What are the most common causes of folate deficiency?

Inadequate dietary intake
Pregnancy
Drugs such as phenytoin or oral contraceptives (they can interfere with folate absorption)

How is folic acid administered?

It is usually given orally.

What is the toxicity of folic acid?

There are no known adverse effects!

ERYTHROPOIETIN

What is erythropoietin?

A glycoprotein normally produced by the kidney

When do you use it?

Erythropoietin is used for the treatment of anemias associated with both end-stage renal failure and bone marrow failure.

What is its toxicity?

The only toxicity is associated with an excessive increase in red blood cell count, which can cause thrombosis and hypertension.

Section V

Respiratory System

Drugs Used to Treat Asthma, Coughs, and Colds

ANTIASTHMATIC DRUGS

What is asthma?

Asthma is a reversible chronic inflammatory disease of the tracheobronchial airways characterized by airflow obstruction and increased responsiveness to a variety of stimuli.

Name the causes of airway obstruction in asthma.

Inflammation of the bronchial wall
Constriction of the bronchiolar smooth muscle
Increased mucus secretion

How is asthma clinically manifested?

Shortness of breath
Coughing
Wheezing
Use of accessory muscles of respiration
Chest tightness

What precipitates an asthma attack?

There are three principal triggers of exacerbations:

1. Allergens—These agents induce mast cell release of inflammatory mediators, such as histamine, leukotrienes, and chemotactic factors, which promote bronchiolar spasm and mucosal thickening.
2. Infections—Viral upper respiratory tract infections are particularly problematic. In children it is common for asthmatic episodes to follow these infections.
3. Psychological factors—These can play a significant role and are often not readily recognized.

List the pharmacologic options for asthma therapy.

Sympathomimetic agents (β_2 -adrenergic agonists)
Corticosteroids
Anticholinergics
Leukotriene inhibitors
Methylxanthines—theophylline
Cromolyn sodium and nedocromil

Which of these drugs are considered safe to use in pregnant women?

All of them; pregnant women with asthma should be treated as aggressively as are nonpregnant asthma patients.

SYMPATHOMIMETIC AGENTS

How do β_2 -adrenergic agonists work?

They work by increasing cyclic adenosine monophosphate (cAMP), which results in bronchodilation.

Name four β_2 -adrenergic agonists that are commonly used for asthma therapy.

1. Pirbuterol (Maxair)
2. Terbutaline (Brethaire)
3. Albuterol (Proventil)
4. Salmeterol (Serevent)—Long acting, **not for acute symptoms**

How are β_2 -adrenergic agonists usually administered?

Most of these drugs are inhaled, which minimizes their systemic side effects because β_2 agonists are poorly absorbed into the circulation via the lungs.

What is their clinical role?

Because they are rapid in onset, β -adrenergic agonists are the drugs of choice for acute relief of bronchospasm.

Are there adverse effects of inhaled bronchodilators?

Yes. The most common are tremor and tachycardia.

CORTICOSTEROIDS

How do steroids work in treating asthma?

Steroids reduce inflammation by:
Reversing mucosal edema
Decreasing the permeability of capillaries
Inhibiting the release of leukotrienes and cytokines

When are corticosteroids used in asthma management?

For both acute and maintenance asthma management:

	Acute exacerbations—Systemic steroids are used, PO or IV depending on the severity.
	Maintenance therapy—Inhaled corticosteroids are used.
Name four inhaled steroids used in the management of chronic asthma.	<ol style="list-style-type: none"> 1. Beclomethasone (Vanceril) 2. Flunisolide (Aerobid) 3. Triamcinolone (Azmacort) 4. Fluticasone (Flovent)
What are the adverse effects of inhaled corticosteroids?	Cough, oral thrush, and dysphonia
What are the adverse effects of systemic corticosteroids such as prednisone?	The list is long and includes abnormalities in glucose metabolism, increased appetite, weight gain, hypertension, and adrenal suppression. (Systemic corticosteroids are further discussed in <i>Chapter 32—Corticosteroids and Inhibitors.</i>)

ANTICHOLINERGICS

How do anticholinergics work?	Parasympathetic stimulation causes bronchial constriction and mucus secretion. Anticholinergics are used to block these responses and maintain bronchial dilation of the airway.
Name an anticholinergic agent used to treat asthma.	Ipratropium (Atrovent), an inhaled anticholinergic
What are its clinical uses?	Treatment of asthma and chronic obstructive pulmonary disease
What side effects may patients experience while using ipratropium?	Dry mouth and sedation. The drug has very few side effects owing to poor systemic absorption.

LEUKOTRIENE INHIBITORS

Describe how leukotriene inhibitors work.	They block the formation of leukotrienes from arachidonic acid (Figure 28–1).
Give two examples of leukotriene inhibitors and state the mechanism of action of each.	<ol style="list-style-type: none"> 1. Zileuton (Zyflo)—5-lipoxygenase inhibitor 2. Zafirlukast (Accolate)—LTD₄ receptor antagonist

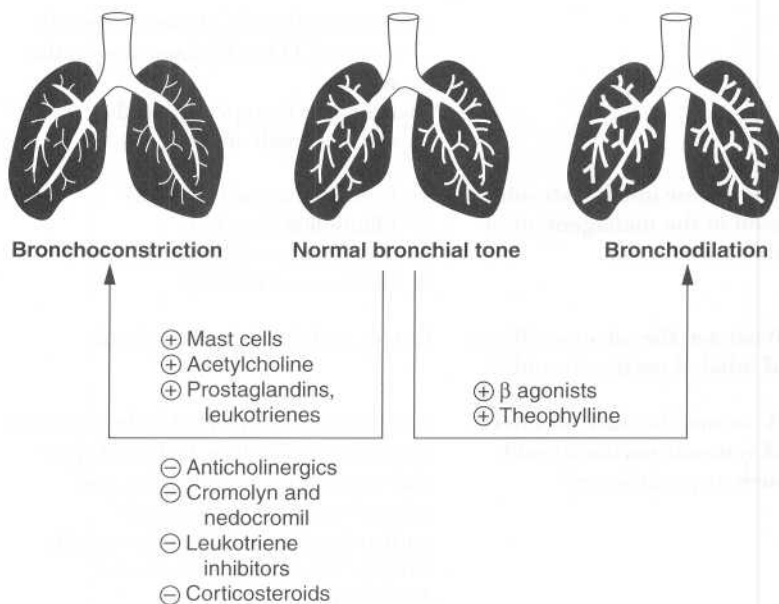


Figure 28-1. Bronchodilation is promoted with the aid of β agonists and theophylline. Bronchoconstriction can be inhibited with the use of anticholinergics, cromolyn, leukotriene inhibitors, and corticosteroids.

What is the route of administration?

Oral

In asthma, what is the clinical role of these drugs?

They prevent bronchoconstriction and airway inflammation. Leukotriene inhibitors are used for chronic maintenance therapy; **they should not be used for acute bronchospasm.**

What are the adverse effects of these drugs?

Zileuton—Some cases of hepatitis have been reported.
Zafirlukast—Drug allergy has been reported.

METHYLSXANTHINES THEOPHYLLINE

What is theophylline and how does it work?

Theophylline is a methylxanthine derivative that increases levels of cAMP

	by inhibiting the enzyme phosphodiesterase, which results in bronchodilation. Theophylline also has some anti-inflammatory effects.
Are there any drug interactions with theophylline?	Cimetidine and erythromycin both increase theophylline plasma levels.
Which drugs decrease plasma levels of theophylline?	Phenytoin and quinolones
What are possible complications with theophylline overdose?	The most common are tremor, insomnia, gastrointestinal distress, and nausea. The most dangerous are seizures and arrhythmias. Methylxanthines are discussed further in <i>Chapter 17—CNS Stimulants</i> .

CROMOLYN SODIUM AND NEDOCROMIL

What are cromolyn sodium (Intal) and nedocromil (Tilade), and how do they work?	They are effective prophylactic agents that stabilize the membranes of mast cells and prevent mediator release, probably by blocking calcium gates.
Can these drugs be used for treating acute attacks of asthma?	No. They are effective prophylactic agents. Pretreatment with cromolyn or nedocromil blocks allergen-induced and exercise-induced bronchoconstriction.
What are the potential toxicities of cromolyn and nedocromil?	Cromolyn—infrequent laryngeal edema, cough, and wheezing Nedocromil—unpleasant taste

ACUTE AND LONG-TERM MANAGEMENT OF ASTHMA

What is status asthmaticus?	A life-threatening attack of asthma
How do you treat status asthmaticus?	IV corticosteroids and bronchodilators are first-line therapy, followed by theophylline.

Which agent is the drug of choice for long-term of asthma in the outpatient setting?

Current recommendations state that patients with mild, persistent symptoms should be started on an inhaled steroid such as fluticasone propionate for routine use. Acute attacks are treated with β_2 -adrenergic agonists.

ANTITUSSIVES (COUGH MEDICATIONS)

When would you use antitussives?

Antitussives have a limited role. Coughing is a symptom and, where possible, therapy is directed to its etiology. However, in acute respiratory tract infections where cough disrupts sleep, antitussives may be used.

How do opiates suppress cough?

Opiates decrease the sensitivity of the central nervous system cough center to peripheral stimuli and decrease mucosal secretion. These actions occur at doses lower than that required for analgesia.

Name three opiates used as antitussives.

1. Codeine
2. Hydrocodone
3. Hydromorphone

What is dextromethorphan?

A synthetic derivative of codeine

How does dextromethorphan work?

It suppresses the response of the cough center, but it does not have any analgesic or addictive potential, and it is less constipating than codeine.

RHINITIS AGENTS

Define rhinitis.

Inflammation of the mucous membranes of the nose

What is its etiology?

Rhinitis is most commonly caused by viruses or by hypersensitivity responses to airborne allergens.

How would you treat this condition?

For allergic rhinitis, try avoidance therapy (avoiding contacts with all known allergens/irritants). If irritant avoidance is not realistically possible, or if the rhinitis appears to be caused by a virus, medical options include:

	<p>Nasal corticosteroids</p> <p>Cromolyn sodium</p> <p>Antihistamines</p> <p>α-adrenergic agonists</p>
Name the corticosteroids commonly used to treat chronic rhinitis.	<p>Beclomethasone and flunisolide. Chronic rhinitis does not show improvement until 2 weeks after the start of therapy.</p>
How do antihistamines work?	<p>Histamine-1 (H_1) receptor blockers are useful in treating the symptoms of allergic rhinitis caused by histamine release.</p>
Name some antihistamines commonly used in the treatment of rhinitis.	<p>Diphenhydramine</p> <p>Chlorpheniramine</p> <p>Cyproheptadine</p> <p>Promethazine</p>
How do α-adrenergic agonists work?	<p>α-adrenergic agonists constrict dilated arterioles in the nasal mucosa and reduce airway resistance. When administered as an aerosol, these drugs have a rapid onset of action and show few systemic effects.</p>
Give two examples of α-adrenergic agonists used in the treatment of rhinitis.	<p>Ephedrine and pseudoephedrine</p>
What happens with prolonged nasal decongestant use?	<p>Rebound nasal congestion often occurs after discontinuation from prolonged use.</p>

Section VI

Endocrine System

29

Hypothalamic and Pituitary Hormones

Define endocrinology.

The study of organs and structures whose function is to secrete into the blood hormones that subsequently elicit a physiologic response

HYPOTHALAMIC HORMONES

What hormones are secreted from the hypothalamus?

The easiest way to remember these hormones is to subdivide them according to function:

Hormones That Affect Growth:

Growth hormone-releasing hormone (GHRH)—GHRH is most often used to stimulate growth hormone release in patients with short stature.

Somatotropin release-inhibiting hormone: somatostatin—

Somatostatin seems to be a generalized inhibiting hormone that is found in both the GI system and CNS, and is known to inhibit the release of insulin, glucagon, and gastrin as well as thyrotropin and growth hormone.

Hormones That Affect Gonadal Function:

Gonadotropin-releasing hormone (GnRH)—If given in pulsatile doses to mimic physiologic cycling, GnRH stimulates the release of follicle-stimulating (FSH) hormone and luteinizing hormone (LH).

Hormones That Affect Corticosteroid Release:

Corticotropin-releasing hormone (CRH)—CRH stimulates the release

of **adrenocorticotrophic hormone (ACTH)** from the anterior lobe of the pituitary through activation of cyclic adenosine monophosphate.

Hormones That Regulate Other Endocrine Organs:

Thyrotropin-releasing hormone (TRH)—TRH is a peptide that stimulates the release of thyrotropin from the anterior lobe of the pituitary. It also stimulates the release of prolactin.

Dopamine—It acts as a natural inhibitor of prolactin release.

How do these hormones work?

The hypothalamic hormones are all peptides that bind to cell surface membrane receptors.

What are these hormones used for?

To test for pituitary insufficiency
For supplemental therapy
For replacement therapy
Bromocriptine, a surface analog of dopamine, is used to treat conditions associated with hyperprolactinemia, such as prolactinoma, acromegaly, and amenorrhea.

Which two hormones are synthesized in the hypothalamus but are not secreted from there?

Oxytocin and vasopressin are synthesized in the hypothalamus but are transported to the posterior pituitary, where they are stored or released from the pituitary into the systemic circulation.

PITUITARY HORMONES

ANTERIOR LOBE PITUITARY HORMONES

What hormones are synthesized and secreted from the anterior lobe of the pituitary (adenohypophysis)?

Growth hormone (GH)
Adrenocorticotrophic hormone (ACTH)
Thyroid-stimulating hormone (TSH)
Follicle-stimulating hormone (FSH)
Luteinizing hormone (LH)
Prolactin (PRL)

What are the clinical uses of these hormones?

Growth hormone—treatment of children with growth hormone deficiency

Adrenocorticotrophic hormone—

diagnosis of adrenal insufficiency

Thyroid-stimulating hormone—

assessment of thyroid dysfunction
(plasma levels are measured)

Follicle-stimulating hormone—used to

treat infertility (stimulates
spermatogenesis in men and
gametogenesis and follicle
development in women)

Luteinizing hormone—used to treat

infertility (stimulates gonadal steroid
production in men and induces
ovulation in women)

**Prolactin—never administered for
therapeutic reasons**

POSTERIOR LOBE PITUITARY HORMONES

**Which two hormones are
released from the posterior
pituitary (neurohypophysis)?**

1. Oxytocin (OXT)
2. Vasopressin (VP)

Oxytocin (Pitocin)

**What are the physiologic
actions of oxytocin?**

Oxytocin stimulates the force and
frequency of uterine contractions. It also
causes milk ejection by contracting myo-
epithelial cells surrounding mammary
alveoli.

State its clinical uses.

Induces and reinforces labor, especially in
patients with delivery complications
Controls postpartum and postabortal
uterine hemorrhage

**State oxytocin's adverse
effects.**

Hypertensive episodes
Uterine rupture

Vasopressin (Antidiuretic Hormone [ADH])

**What are vasopressin's
mechanisms of action?**

Vasopressin activates V_2 receptors in the
collecting tubules to increase water
permeability and water resorption. This
results in concentrated urine.

What are vasopressin's clinical uses?

Central diabetes insipidus—
ADds Hydration to the body
Control of variceal or colonic
bleeding through its vasocon-
strictive properties



What are the adverse effects of this drug?

Headache
Nausea and abdominal cramps
Hypertension
Bradycardia

Desmopressin

What is it?

Desmopressin is a long-acting synthetic analogue of vasopressin that activates V_2 receptors on the renal tubule cells to increase water permeability and resorption. It has minimal effect on V_1 receptors which mediate vasoconstriction.

What are desmopressin's therapeutic uses?

Central diabetes insipidus
Nocturnal enuresis

What are its adverse effects?

Headache
Nausea, abdominal pain and cramps
Hyponatremia at high doses
bradycardia

30

Thyroid and Antithyroid Drugs

Name three major hormones secreted by the thyroid gland.

1. Thyroxine (T_4)
2. Triiodothyronine (T_3)
3. Calcitonin

What are the physiologic controls of the thyroid gland?

Thyroid-stimulating hormone (TSH)
from the hypothalamus
Thyrotropin-releasing hormone (TRH)
from the pituitary
Feedback from T_3 and T_4

What is the basic structure of the thyroid gland?

The thyroid gland is composed of multiple follicles, each of which has a lumen filled with thyroglobulin (colloid), the storage form of thyroid hormone. The follicles are surrounded by parafollicular cells that produce calcitonin.

How are T_3 and T_4 formed?

The tyrosine residues of thyroglobulin are iodinated in the gland to form mono-iodotyrosine (MIT) or diiodotyrosine (DIT). T_4 is a combination of two DIT molecules, and T_3 is a combination of one MIT and one DIT molecule. See Figure 30-1.

Which is more potent— T_3 or T_4 ?

T_3 is 10 times more potent than T_4 . In fact, most of the systemic effects of the thyroid hormones are due to T_3 , because T_4 is converted to T_3 in the peripheral tissues, liver, and kidneys.

How are T_3 and T_4 transported within the body?

Thyroid hormones are largely bound to thyroxine-binding globulin (TBG). Only 0.04% of T_4 and 0.4% of T_3 exist in the free form, and only the free form has metabolic activity.

Where do T_3 and T_4 bind?

The receptors that bind thyroid hormone are located within the nucleus of the cell.

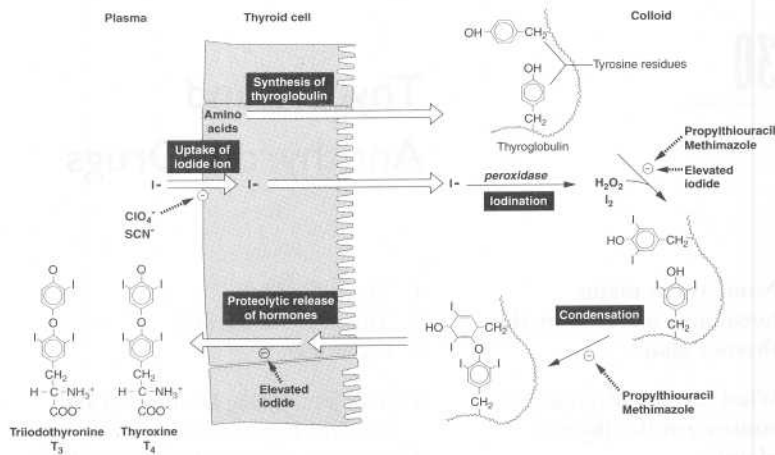


Figure 30-1. Biosynthesis of thyroid hormones. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 252.)

HYPOTHYROIDISM

What are the symptoms of hypothyroidism?

Hypothyroidism affects almost every system in the body. The most common presenting signs, however, are:

- Fatigue
- Cold intolerance
- Weight gain despite reduced appetite
- Irregular menses
- In severe cases the skin may show nonpitting edema (myxedema).

What diseases and conditions commonly cause hypothyroidism?

Hashimoto's thyroiditis (an autoimmune disorder)

- Drugs or radiation exposure
- Pituitary tumors

What are the treatment options for hypothyroidism?

Levothyroxine sodium—drug of choice because of its consistent potency and prolonged duration of action

- Liothyronine sodium

LEVOTHYROXINE SODIUM (T_4 SYNTHROID)

What are the major indications for thyroxine administration?

Hypothyroidism

- Prevention of mental retardation in newborns with thyroid deficiency

(infantile hypothyroidism)—This condition may be avoided if thyroid supplementation occurs within the first 2 weeks of life.

TSH suppression therapy after treatment for thyroid cancer

How is levothyroxine absorbed and metabolized?

Levothyroxine is absorbed from the small intestine and is metabolized in the liver. It has a half-life of 7 days.

What are its adverse effects?

Tachycardia
heat intolerance
Tremors

LIOTHYRONINE SODIUM (T₃ CYTOMEL)

What are the clinical indications for this drug?

Liothyronine sodium is usually reserved for the treatment of myxedema coma in combination with levothyroxine. Symptoms of myxedema coma, which is a medical emergency include hypothermia, respiratory depression, and unconsciousness.

What are the toxicities of liothyronine?

Similar to those of levothyroxine but is more cardiotoxic

HYPERTHYROIDISM

What are the symptoms of hyperthyroidism?

In general, the symptoms are the opposite of those seen in hypothyroidism. The most common presenting symptoms are:
Nervousness
Sweating
Hypersensitivity to heat
Weight loss despite increased appetite

What is the most common cause?

Graves' disease, an autoimmune disorder in which a thyroid-stimulating immunoglobulin causes thyrotoxicosis

What are some other causes?

Toxic multinodular goiter
Subacute thyroiditis

What are the treatment options?

Propylthiouracil and methimazole
Iodine salts
Ionic inhibitors
Radioactive iodine
Surgery

PROPYLTHIOURACIL AND METHIMAZOLE

What are they?	Sulfur-containing molecules known as thioamides
How do they work?	They stop the iodination and coupling of the thyroglobulin molecule. Therefore, MIT and DIT cannot be produced. Without MIT and DIT, it is impossible to produce T_3 and T_4 (see Figure 30–1).
What is the route of administration?	Oral
What are the adverse effects?	Agranulocytosis (rare, but most important effect to watch for) Rash (common) Edema

IODIDE (IODINE SALTS)

What is the difference between iodine and iodide?	Iodide is the ionic form of the element iodine.
Why give iodides?	Giving iodides would seem intuitively to exacerbate symptoms of hyperthyroidism. However, giving iodides in large doses actually decreases release of thyroid hormone. Iodides also decrease the vascularity and size of the thyroid gland.
In what situations do you use iodides?	Iodides today are rarely used as sole therapy. Most often they are used before surgery or in conjunction with a thioamide and propranolol in thyrotoxic crisis.
Give two examples of available iodide preparations.	1. Lugol's solution—a mixture of iodine and potassium iodide 2. Potassium iodide
What are the adverse effects of iodides?	Anaphylactoid reaction—angioedema and swelling of the larynx Chronic iodide intoxication (iodism) Brassy taste and burning in the mouth Soreness of the teeth and gums Swelling of the eyelids Coryza and sneezing that simulates a cold Respiratory problems Enlarged parotid and submaxillary glands

IONIC INHIBITORS

Give two examples of Ionic inhibitors.	Perchlorate (ClO_4^-) and thiocyanate
What is their mechanism of action?	They competitively inhibit the concentration of iodide by blocking the iodide transport mechanism.
What are the clinical uses of the Ionic inhibitors?	Ionic inhibitors have been used in the past to treat Graves' disease and amiodarone-induced thyrotoxicosis. However, their use has diminished in favor of other options.

RADIOACTIVE IODINE

Why use radioactive iodine (I_{131})?	Because the thyroid gland very avidly takes up iodine, a dose of radioactive iodine can ablate thyroid tissue, which results in <i>permanent</i> reduction of thyroid activity.
In whom do you use it?	In adults over the age of 21 who have hyperthyroidism. It is also the best form of treatment when Graves' disease has been refractory to antithyroid drugs or has persisted after subtotal thyroidectomy.
Is there any evidence that iodine causes cancer?	No
What are the adverse effects?	A high incidence of delayed hypothyroidism
What are the contraindications?	Radioactive iodine should not be used in pregnant women or nursing mothers.

THYROID STORM

What is it?	A life-threatening medical emergency characterized by extreme effects of hyperthyroidism.
What causes it?	Illness, surgery, or other stress in a patient who is already thyrotoxic

How do you manage a patient who has thyroid storm?

β -Adrenergic blockers to manage hypertension and tachycardia
 Propylthiouracil or methimazole
 Intravenous sodium iodine
 Glucocorticoids to inhibit peripheral conversion of T_4 to T_3

31

Sex Steroids and Inhibitors

What are the three major categories of sex steroids?

1. Estrogens
2. Progestins
3. Androgens

How do natural estrogens, progestins, and androgens work?

In general, because all of these agents are steroids, the compounds will enter the cell and bind to a cytosolic receptor. The ligand receptor complex will then travel to the nucleus of the cell and activate gene transcription.

ESTROGENS

What are estrogens?

The estrogens are compounds that are involved in normal female development and regulation of the menstrual cycle.

What are the three main estrogens produced by the female body?

1. Estradiol
2. Estrone
3. Estriol

Which of these estrogens is the principal secretory product of the ovary?

Estradiol

What are the precursors to estrogen synthesis?

Androstenedione and testosterone (Figure 31-1)

What are estrogen's most important physiologic effects?

Regulates growth and maturation of reproductive organs
Stimulates endometrial growth
Reduces bone resorption and maintains normal structure of the skin and blood vessels
Increases levels of thyroxine-binding globulin

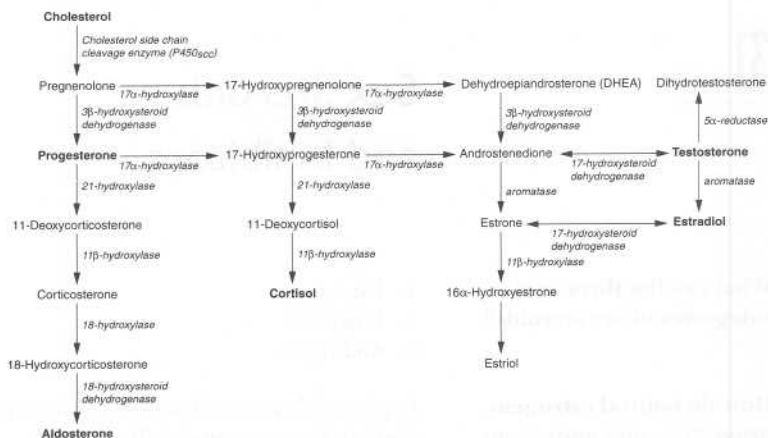


Figure 31-1. Steroid hormone synthesis. (Redrawn from Gallia G, Hann CL, Hewson WH: *The Pharmacology Companion*. Alert & Oriented Publishing Company, 1997, Fig 7.2.)

Increases HDL and triglyceride levels,
and decreases LDL levels
Promotes coagulation of blood

**Give examples of estrogens
that are currently used
clinically.**

Estradiol (Estrace)
Conjugated estrogens (Premarin)
Ethinyl estradiol (Estinyl)
Quinestrol (Estrovis)

**What are the clinical uses
of estrogens?**

An important therapeutic use of estrogens is treatment of hypogonadism in girls.
Estrogens are used in oral contraceptives in combination with progestins. They suppress FSH secretion and therefore inhibit ovulation.
Estrogens are used in postmenopausal hormone replacement therapy. They help reduce the risk of cardiovascular disease, osteoporosis, hot flashes, and vaginitis.
They are used in the treatment of prostate cancer.

**What is the route of
administration?**

Estrogens are effective when given transdermally, intramuscularly, and orally.

What are the potential toxic effects of estrogen replacement?

Postmenopausal bleeding
Endometrial hyperplasia
Breast tenderness
Cholestasis
Over long periods there is an increased risk of hypertension, thromboembolism, hepatic adenoma, and breast and endometrial cancer.

Name four *absolute* contraindications to estrogen replacement therapy.

1. Breast cancer
2. Pregnancy
3. Liver disease
4. History of thrombophlebitis

ESTROGEN INHIBITORS

TAMOXIFEN (NOLVADEX)

What is tamoxifen?

A nonsteroidal that acts as a competitive inhibitor of estradiol by binding to the estrogen receptor

When is it used?

Treatment of breast cancer in postmenopausal women

Are there adverse effects?

Yes—hot flashes, nausea, and vomiting

CLOMIPHENE (CLOMID)

Describe this drug.

Clomiphene is a partial agonist at estrogen receptors in the pituitary gland. This drug prevents the normal feedback inhibition, and increases release of LH and FSH from the pituitary, which subsequently stimulates ovulation.

How is clomiphene used therapeutically?

To treat infertility

What are the adverse effects?

Hot flashes
Ovarian enlargement
Multiple simultaneous births
Visual disturbances

PROGESTINS

Name the most important progestin of the human body.

Progesterone is the prototypical progestin. It is synthesized in the ovary, testis, and adrenal gland from circulating cholesterol (see Figure 31–1).

What are the physiologic effects of progesterone?

Stimulates lipoprotein lipase activity and increases fat deposition
Increases insulin response to glucose
Promotes glycogen storage in the liver
Increases body temperature
Regulates maturation of the endometrium
Also regulates development of breast secretory glands

Give some examples of synthetic progestins.

Medroxyprogesterone acetate (Provera)
Norethindrone (Norlutin)
Norethindrone acetate (Aygestin)

What are the therapeutic uses of progestins?

Contraception—used either alone or with estradiol
Hormone replacement therapy, in combination with estrogen
Also used when **ovarian suppression** is necessary, for example, in the treatment of dysmenorrhea and endometriosis
Diagnosis of estrogen secretion—If menstruation occurs after administration of progesterone in amenorrheic patients, it can be concluded that the uterus has been stimulated by estrogen.

How can progestins be administered?

Orally or by IM injection

Describe the adverse effects.

Weight gain
Depression
Edema
Acne
Hypertension
Thrombophlebitis
Cholestatic jaundice

PROGESTIN INHIBITORS—MIFEPRISTONE (RU 486)

Describe mifepristone.

It is a competitive inhibitor of progestins at progesterone receptors.

When do you use it?

This controversial “morning after” drug is used as an abortifacient. It is usually given concomitantly with prostaglandin E or prostaglandin F to increase myometrial contractions.

Are there adverse effects? Yes—heavy bleeding, GI effects (nausea, vomiting, anorexia), and abdominal pain

DANAZOL (DANOCRINE)

Describe danazol. Danazol is a drug that acts as a partial agonist at progesterone, androgen, and glucocorticoid receptors.

When is it used? The drug is used to treat endometriosis.

What are the adverse effects? Weight gain
Edema
Acne
Reduced HDL cholesterol levels

ANDROGENS

What are androgens? Androgens are a group of 19-carbon steroids derived from cholesterol.

Name four androgens produced by the testes?

1. Testosterone
2. Dihydrotestosterone
3. Dehydroepiandrosterone
4. Androstenedione

See Figure 31–1.

Which is the principal androgen? Testosterone

Where is testosterone produced? In the testis, the adrenal gland, and (to a small degree) the ovary

What is testosterone produced from? Progesterone and dehydroepiandrosterone

What are the physiologic effects of the androgens? The androgens' effects can be broken down into two categories:

1. Anabolic—increase in muscle mass and red blood cell production
2. Androgenic—growth of the larynx and skeleton, development of facial hair, darkening of skin

Give some examples of synthetic androgens. Oxandrolone (Oxandrin)
Stanozolol (Winstrol)
Fluoxymesterone (Halotestin)
Oxymetholone (Anadrol-50)
Nandrolone phenpropionate (Durabolin)

What are the clinical uses of synthetic androgens?

Replacement therapy in hypogonadism
Osteoporosis
Can be used as growth stimulators

Describe the toxicities of synthetic androgen treatment.

Toxicity is mostly related to over-masculinization. In women, excessive testosterone can lead to hirsutism, depression of menses, acne, and clitoral enlargement. Very rarely, hepatic adenomas and carcinomas have been reported. Cholestatic jaundice and prostatic hypertrophy can also occur.

Name a contraindication to androgen use.

Pregnancy

ANDROGEN ANTAGONISTS

Name the four categories of androgen antagonists and give examples of each.

1. Gonadotropin-releasing analogues—leuprolide or gonadorelin
 2. Receptor inhibitors—cyproterone and flutamide
 3. Steroid synthesis inhibitors—ketoconazole, spironolactone
 4. 5α -reductase inhibitors—finasteride
- See Figure 31-2.

What are androgen antagonists used for?

Treatment of benign prostatic hyperplasia as well as hirsutism, (fina steride) in women (cyproterone spironolactone), prostatic cancer (leuprolide), and Cushings disease (ketoconazole).

FEMALE CONTRACEPTION

What are the three different kinds of oral contraceptives currently available?

1. Combination estrogen-progestin tablets that are taken in constant doses throughout the menstrual cycle
2. Combination estrogen-progestin in which the progestin concentration slowly increases to mimic the natural cycle
3. Progestin-only preparations

What kinds of implantable or injectable contraception are currently available?

These are primarily progestin-only agents. Examples include norgestrel (Norplant) and Progestasert, a intrauterine device that releases low amounts of progesterone over the course of a few years.

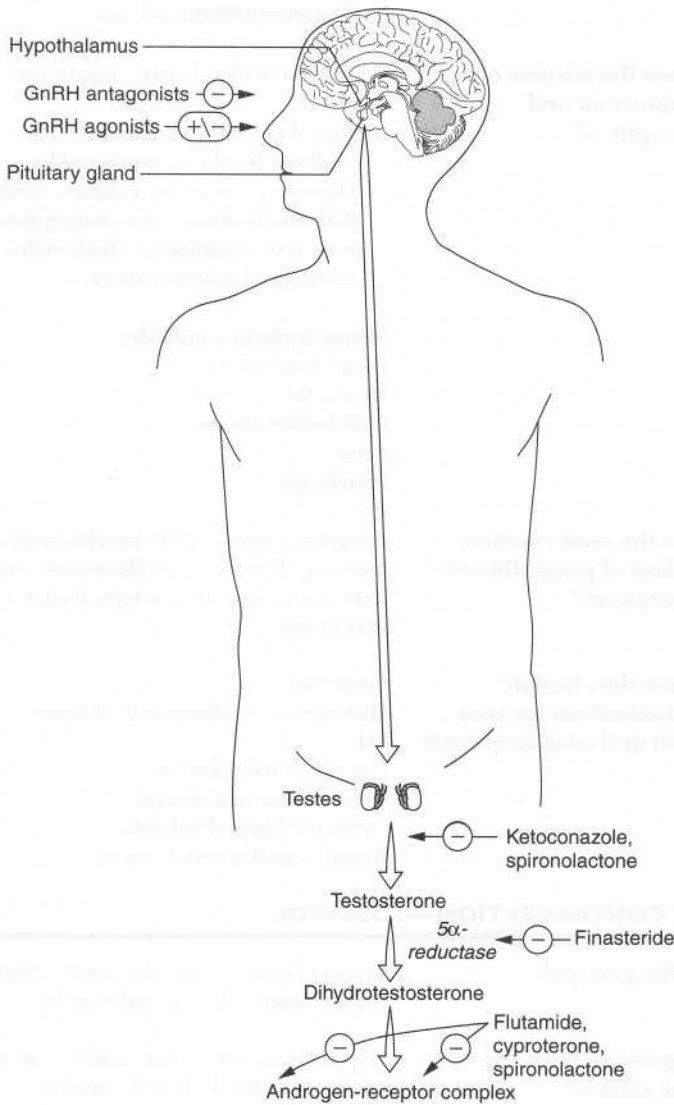


Figure 31-2. Sites of action of some antiandrogen drugs.

How do oral contraceptives work?

They work primarily by preventing ovulation. In addition, they change the properties of cervical mucus and impair implantation of fertilized ova.

What are the adverse effects of combination oral contraceptives?

Formation of blood clots—major toxic effect
Increased risk of breast cancer—The evidence for this is *questionable*.
However, *convincing evidence* exists that combination oral contraceptives *reduce* the incidence of both endometrial and ovarian cancer.

Minor toxicities include:

Breast tenderness
Headache
Gallbladder disease
Acne
Weight gain

What is the most common side effect of progestin-only contraceptives?

Irregular, unpredictable breakthrough bleeding. The incidence decreases over time, and amenorrhea is typical after 1 year of use.

What are the absolute contraindications for combination oral contraceptives?

Pregnancy
History of thromboembolic disease
MI
Coronary artery disease
Cerebral vascular disease
Congenital hyperlipidemia
Breast or endometrial cancer

MALE CONTRACEPTION—GOSSYPOL

Describe gossypol.

Gossypol is a cottonseed derivative that reduces sperm density and motility.

Does gossypol have any adverse effects?

Hypokalemia, which may lead to transient weakness or paralysis, is the major adverse effect.

32

Corticosteroids and Inhibitors

What are the two major groups of corticosteroids?

Mineralocorticoids and glucocorticoids

Where are corticosteroids produced?

In the adrenal cortex—specifically in the zona glomerulosa (mineralocorticoids) and the zona fasciculata (glucocorticoids)

Describe the functions of the two major pharmacologic groups of corticosteroids.

1. **Glucocorticoids**—primarily affect metabolism, inflammation, and immune responses
2. **Mineralocorticoids**—affect fluid and electrolyte balance

The biologic activity of the synthetic corticosteroids discussed here ranges from strict glucocorticoid to strict mineralocorticoid activity (Figure 32–1).

How are corticosteroids administered?

Most can be given orally, topically, or via IM injection. Prednisone is only administered orally.

GLUCOCORTICOIDS

How do glucocorticoids work?

Both glucocorticoids and mineralocorticoids enter the cell and bind to a cytosolic receptor. The steroid receptor complex then enters the nucleus and activates gene expression by binding to specific DNA receptors.

What are the major physiologic effects of glucocorticoids?

Anti-inflammatory effects—

Glucocorticoids inhibit the number and function of lymphocytes, eosinophils, basophils, and monocytes; increase neutrophils at the site of injury; and inhibit the release of arachidonic acid, the major precursor to prostaglandins, by blocking the enzyme phospholipase A₂.

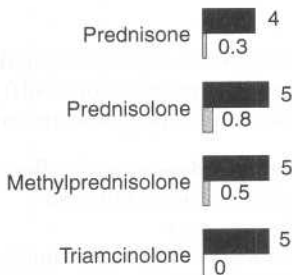
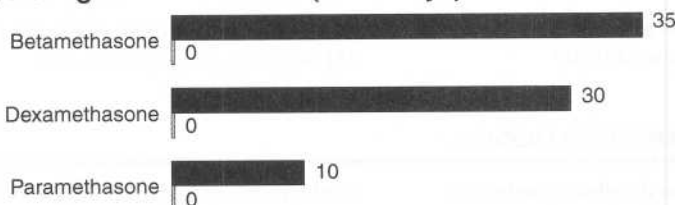
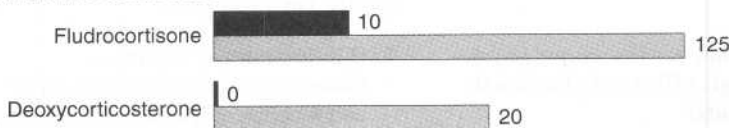
Short-Acting Glucocorticoids (8 – 12 hr)**Intermediate-Acting Glucocorticoids (18 – 36 hr)****Long-Acting Glucocorticoids (1 – 3 days)****Mineralocorticoids**

Figure 32-1. Pharmacologic properties of some commonly used natural and synthetic corticosteroids. Activities are all relative to hydrocortisone = 1. Time refers to duration of action. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 255.)

Metabolic effects—Glucocorticoids stimulate gluconeogenesis, lipolysis, and lipogenesis, resulting in an increase in plasma glucose levels that provides energy for the body to fight infection, trauma, debilitating disease, or other stresses.

Catabolic effects—Glucocorticoids can cause muscle, bone, lymphoid, skin, and fat catabolism.

Immunosuppressive effects—Glucocorticoids inhibit the function of lymphocytes, monocytes, and eosinophils.

Name the major natural glucocorticoid of the human body. Cortisol

What hormone normally controls cortisol secretion? Adrenocorticotrophic hormone (ACTH)

How is cortisol transported in the blood? Ninety percent of cortisol is bound to plasma proteins.

How is cortisol metabolized? Primarily in the liver

Does cortisol have any mineralocorticoid properties? Yes! This is an important reason for the hypertension associated with Cushing's syndrome.

Name the major synthetically produced glucocorticoids. Prednisone (Orasone, Deltasone)
Triamcinolone (Aristocort)—often used topically
Dexamethasone (Decadron)
Beclomethasone (Beclivent)
Betamethasone (Celestone)

How do the synthetically produced glucocorticoids differ from one another and from naturally occurring glucocorticoids? They differ in respect to half-life and the ratio of glucocorticoid-to-mineralocorticoid activity. In general, the synthetic agents are longer acting (Figure 32-1) and have better absorption through lipid barriers.

What are the therapeutic uses of synthetic glucocorticoids? Adrenal insufficiency (Addison's disease)—in conjunction with a mineralocorticoid

Congenital adrenal hyperplasia
 Asthma (beclomethasone)
 Collagen vascular diseases
 Ocular disease—uveitis, exophthalmos,
 optic neuritis
 Lung maturation in a fetus
 (betamethasone)—helps increase
 production of surfactant
 Skin disease—contact dermatitis,
 urticaria
 Chemotherapy—prednisone for
 Hodgkin's disease
 Diagnosis of Cushing's syndrome—
 dexamethasone suppression test
 Cerebral edema—dexamethasone
 Inflammation reduction in general—
 rheumatoid arthritis and osteoarthritis,
 inflammatory bowel disease

What are the adverse effects of glucocorticoids?

Long-term use of glucocorticoids can cause a large number of side effects. The most important include:
 Adrenal suppression
 Metabolic disorders including diabetes, muscle wasting, and osteoporosis
 CNS effects such as a psychosis or euphoria
 Stimulation of peptic ulcers
 Iatrogenic Cushing's syndrome—weight gain, moon face, acne, increased body hair growth
 To avoid these effects, it is important to *use as low a dose as possible* and to *taper the steroids* after achieving a therapeutic response.

MINERALOCORTICIDS

What is the major mineralocorticoid in the body?

Aldosterone

What controls the secretion of aldosterone?

ACTH and the renin-angiotensin system

Describe the function of aldosterone.

Aldosterone acts on the renal tubule cells to increase reabsorption of sodium, bicarbonate, and water in exchange for the excretion of potassium.

Name some synthetic mineralocorticoids.	Fludrocortisone (Florinef) Desoxycorticosterone
What are mineralocorticoids responsible for?	Fluid and electrolyte balance, especially of sodium and potassium
What is fludrocortisone used for?	Replacement therapy after adrenalectomy or for primary and secondary adrenocortical insufficiency
What side effects can be seen with fludrocortisone therapy?	Hypokalemia Congestive heart failure due to volume overload

ADRENOCORTICOSTEROID ANTAGONISTS

Do adrenocorticosteroid antagonists inhibit both glucocorticoid and mineralocorticoid activity?	Yes
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AMINOGLUTETHIMIDE (CYTADREN)

How does aminoglutethimide work?	It inhibits cytochrome P-450, which catalyzes the rate-limiting step of conversion of cholesterol to pregnenolone. This reduces the biosynthesis of all physiologic steroids.
How is it used?	To decrease hypersecretion of cortisol in patients who have Cushing's syndrome To reduce estrogen production in the treatment of breast cancer (commonly used with dexamethasone)
Are there adverse effects?	Yes. Gastrointestinal and neurologic side effects are seen, along with a transient maculopapular rash.

METYRAPONE (METOPIRONE)

What is the action of this drug?	It reduces corticosteroid biosynthesis by inhibiting the cytochrome P-450 system.
What are the clinical uses?	Testing adrenal function
What are the side effects of metyrapone?	Hirsutism Salt and water retention

KETOCONAZOLE (NIZORAL)

What is the role of ketoconazole?

Although ketoconazole is mainly used as an antifungal agent, it also inhibits steroid synthesis, so it has been used to treat Cushing's syndrome. See *Chapter 46—Antifungal Drugs* for further details.

33

Insulins and Oral Hypoglycemic Drugs

TREATMENT STRATEGIES FOR DIABETES

What is the general treatment strategy for insulin-dependent diabetes (Type 1)?

Patients with this disease have an absolute deficiency of insulin because of enormous β -cell destruction. Treatment includes:
Dietary and exercise instruction
Parenteral insulin (usually a mix of regular and NPH to match physiologic outputs)

What is the general treatment strategy for non-insulin-dependent diabetes (Type 2)?

This disease is frequently associated with low-to-normal insulin levels and target organ insulin resistance. Treatment includes:
Dietary modification
Weight reduction
Oral hypoglycemic agents
Parenteral insulin for cases that are unresponsive to all of the above.

INSULIN

What is the structure of insulin?

It is a 51 amino acid protein consisting of two polypeptide chains connected by disulfide bonds

Where does insulin work?

Insulin binds to proteins in the circulation and cell membrane receptors. Insulin does **not** enter the cell nucleus.

What type of receptor does insulin bind to?

Tyrosine kinase

What are the effects of insulin?

Insulin affects almost every tissue in the body, but the most important target organs are:

Liver—promotes glucose storage as glycogen; increases triglyceride synthesis

Muscle—facilitates protein and glycogen synthesis

Adipose tissue—improves triglyceride storage by activating plasma lipoprotein lipase; reduces circulating free fatty acids

What are the types of insulin preparations used clinically?

There are three main classes of insulin:

1. **Short-acting**—insulin lispro (Humalog) and regular (Humulin)
2. **Intermediate-acting**—isophane insulin suspension (neutral protamine Hagedorn [NPH] insulin) and insulin zinc suspension (lente)
3. **Long-acting**—insulin zinc suspension extended (ultralente)

Protamine and Semilente insulin are no longer used in the United States.

Which types of insulin are used for management of hyperglycemic emergencies?

Lispro and regular, because they can be given intravenously and work rapidly

What are the sources of insulin?

Animal insulin preparations are made from beef and pork. Human insulin can be made through bacterial DNA recombinant technology.

What determines the onset, peak, and duration of action of a particular type of insulin preparation?

The mixture ratio of zinc protamine and other substances to insulin determines the rate of release (Table 33-1).

What is the standard route for the administration of insulin?

Subcutaneous injection

What are adverse effects of insulin use?

Symptoms of hypoglycemia—diaphoresis, vertigo, tachycardia

Insulin allergy—an immunoglobulin E-mediated reaction

Insulin antibodies—immunoglobulin G-mediated

Lipodystrophy—a change in the fatty tissue surrounding the injection site

Table 33–1. Pharmacokinetics and Compatibility of Various Insulins

	Insulin Preparations	Onset	Peak	Duration	Compatible mixed with
Rapid-Acting	Insulin Injection (Regular)	0.5 to 1		8 to 12	All
	Lispro Insulin Solution	0.25	0.5 to 1.5	6 to 8	Ultralente, NPH
Intermediate-Acting	Isophane Insulin Suspension (NPH)	1 to 1.5	4 to 12	24	Regular
	Insulin Zinc Suspension (Lente)	1 to 2.5	7 to 15	24	Regular, semilente
Long-Acting	Extended Insulin Zinc Suspension (Ultralente)	4 to 8	10 to 30	> 36	Regular, semilente

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ORAL HYPOGLYCEMIC AGENTS

What are the four major classes of oral hypoglycemic agents?

1. Sulfonylureas
2. Biguanides
3. α -glucosidase inhibitors
4. Thiazolidinedione

Can these classes be used in combination to achieve glycemic control?

Yes. For example, a sulfonylurea may be used with a biguanide.

SULFONYLUREAS

Give examples of sulfonylureas.

Chlorpropamide (Diabinese)—first generation; has the longest duration of action
 Tolbutamide (Orinase)—first generation
 Acetohexamide (Dymelor)—first generation
 Glyburide (Micronase)—second generation; high potency
 Glipizide (Glucotrol)—second generation; high potency
 Glimepiride (Amaryl)—second generation

How do sulfonylureas work?

They stimulate the release of endogenous insulin from β cells of the pancreas and increase binding of insulin to target tissues and receptors. The initial step in the facilitation of endogenous insulin release is binding to and blocking receptors on adenosine triphosphate-sensitive K^+ channels.

What are the adverse effects of sulfonylureas?

Hypoglycemia due to an overdose—most important
 Gastrointestinal distress
 Pruritus
 Nausea
 Agranulocytosis and aplastic anemia (rare)
 Chlorpropamide in particular has a tendency to decrease ethanol tolerances and cause water retention.
 In general, adverse effects occur slightly less often with second generation sulfonylureas.

What are the pharmacokinetics of the sulfonylureas?	These agents are metabolized in the liver and excreted by the kidneys. (Glyburide is also eliminated through feces.)
What are contraindications to the use of sulfonylureas?	Liver or renal insufficiency
What drugs potentiate the effects of sulfonylureas?	Aspirin Monoamine oxidase inhibitors Ethanol Phenylbutazone Probenecid Allopurinol Anticoagulants
What drugs <i>reduce</i> the effects of sulfonylureas?	Phenobarbital β -adrenergic blockers Rifampin Cholestyramine Loop and thiazide diuretics

BIGUANIDES

Name two biguanides.	1. Metformin (Glucophage) 2. Phenformin—withdrawn owing to an association with severe lactic acidosis
What is their mechanism of action?	The mechanism is not known for certain. However, several proposed theories include stimulation of glycolysis in peripheral tissues and reduced hepatic gluconeogenesis.
Does metformin cause a hypoglycemia?	No, not even in large doses
What are the contraindications to the use of metformin?	Renal or liver disease Cardiac failure Chronic hypoxic lung disease It is also recommended that metformin be withheld prior to a radiologic procedure using IV iodinated contrast medium because of the potential for acute renal failure induced by the contrast medium.
How is metformin metabolized?	It is excreted unchanged in the urine and does not undergo hepatic metabolism. Tubular secretion is the major route of elimination.

What are the adverse effects?

Lactic acidosis
Gastrointestinal reactions (diarrhea, nausea, upset stomach)
Decreased absorption of vitamin B₁₂ and folate may occur with long-term therapy.

α-GLUCOSIDASE INHIBITOR ACARBOSE (PRECOSE)

What is acarbose's mechanism of action?

This drug delays the absorption of glucose from the gastrointestinal tract.

What is its advantage over other oral hypoglycemic agents?

It does not cause a reactive hypoglycemia.

How is it metabolized?

Acarbose is metabolized exclusively within the GI tract, mostly by intestinal bacteria but also by digestive enzymes. Approximately one third of the drug is excreted in the urine.

What are the adverse effects?

Gastrointestinal symptoms (flatulence, bloating, diarrhea)

THIAZOLIDINEDIONE DERIVATIVES

Give one example of this class.

Troglitazone (Rezulin)

How does this drug work?

Troglitazone lowers blood glucose by improving target cell response to insulin. It is dependent on the presence of insulin for its activity. It decreases hepatic glucose output and increases insulin-dependent glucose disposal in skeletal muscle.

Where in the cell does it act?

The mechanism is thought to involve binding to nuclear receptors that regulate the transcription of a number of insulin-responsive genes.

How is troglitazone metabolized?

By the cytochrome P-450 system

What are the adverse effects?

Troglitazone has a fairly safe profile. Adverse effects include hepatotoxicity, hypoglycemia and headache.

34

Drugs That Affect Calcium Homeostasis

What is the major storage reservoir of calcium and phosphorus in the body?

Bone

Name the principal regulators of plasma Ca^{2+} levels within the body.

PTH
Vitamin D
Calcitonin

HYPOCALCEMIA

What are the most common presenting signs of hypocalcemia?

Muscular excitability—tetany
Paresthesias
Laryngospasm
Seizures
Chvostek's and Trousseau's signs

What is Chvostek's sign?

Facial muscle spasm that occurs when the facial nerve is tapped anterior to the ear.

What is Trousseau's sign?

Carpal spasm after occluding blood flow in the forearm with a blood pressure cuff

What are the most common causes of hypocalcemia?

Chronic renal failure
Hypoparathyroidism
Vitamin D deficiency
Malabsorption

What are the pharmacologic treatment options available for hypocalcemia?

Calcium salt preparations
Vitamin D preparations

CALCIUM SALT PREPARATIONS

Name four of the more common calcium salt preparations that are available.

1. Calcium chloride (Tums)
2. Calcium gluceptate
3. Calcium gluconate
4. Calcium carbonate

What are the adverse effects of calcium supplementation?

Calcium supplements may cause peripheral vasodilation or transient tingling. Also, rapid infusion of calcium can cause cardiac arrhythmias.

VITAMIN D AGENTS

Name three of the more common vitamin D agents currently available.

1. Calcitriol (Calcijex)-the vitamin D metabolite of choice for quickly raising serum calcium levels
2. Ergocalciferol (Drisdol)
3. Calciferol

How does vitamin D work?

It stimulates absorption of calcium and phosphate from the intestine, and also decreases the renal excretion of calcium.

What are the common clinical indications for the use of vitamin D supplements?

Osteoporosis, chronic renal failure, nutritional rickets (caused by inadequate dietary intake of vitamin D), metabolic rickets (caused by tissue resistance to vitamin D), osteomalacia, hypoparathyroidism

What are the side effects of these agents?

Vascular calcification, nephrocalcinosis, and soft-tissue calcification

HYPERCALCEMIA

What are the most common symptoms of hypercalcemia?

Usually the patient is asymptomatic; however, patients may demonstrate weariness, renal stones, constipation, abdominal pain, weakness, confusion, and delirium—"Groans, bones, and psychiatric overtones."



What conditions or diseases will cause hypercalcemia?

CHIMPANZEES:
 Calcium supplementation
 Hyperparathyroidism
 Iatrogenic (caused by thiazide diuretics)
 Milk alkali syndrome / Malignancy
 Paget's disease
 Addison's disease
 Neoplasm
 Zollinger-Ellison syndrome
 Excess vitamin D
 Excess vitamin A
 Sarcoid

List the pharmacologic treatment options that are available to treat hypercalcemia.

Rehydration with saline and diuresis with loop diuretics; bisphosphonates, calcitonin, gallium nitrate, plicamycin, glucocorticoids

BISPHOSPHONATES

Give two examples of drugs in this category.

Etidronate and pamidronate

How do these drugs work?

They inhibit osteoclastic activity—more specifically, they reduce both the resorption and formation of hydroxyapatite crystals.

What is their route of administration?

Pamidronate—IV only
Etidronate—oral or IV

When are bisphosphonates used?

Malignancy-associated hypercalcemia
Paget's disease of the bone
Osteoporosis

What are the adverse effects?

Bone pain in patients who have Paget's disease, usually around the pagetic lesion; osteomalacia; nausea and diarrhea

CALCITONIN (CALCIMAR)

What is it?

A 32-amino-acid peptide synthesized and secreted by the parafollicular C cells of the thyroid gland

What are the physiologic actions of calcitonin?

It decreases osteoclastic bone resorption as well as calcium and phosphate reabsorption from the kidney.

When is calcitonin used?

For Paget's disease, hypercalcemia, and osteoporosis

What type of calcitonin is used?

Although human calcitonin is available, salmon calcitonin is often used because it is more potent and has a longer half-life.

What are the adverse effects?

Allergic reaction, GI effects, and flushing, redness, or tingling of the face

GALLIUM NITRATE (GANITE)

How does it work?

Gallium nitrate decreases serum calcium levels by inhibiting bone resorption.

What is the indication for use? Hypercalcemia associated with malignancy

Does this drug have any adverse effects? Yes—nephrotoxicity

PLICAMYCIN (MITHRACIN)

What is plicamycin? A cytotoxic antibiotic that also lowers serum calcium concentration

How does it work? Plicamycin is thought to lower serum calcium levels by either inhibiting the effect of parathyroid hormone on osteoclasts, or blocking the effects of vitamin D.

When is it used? For malignancy-associated hypercalcemia and Paget's disease of the bone

What are the adverse effects? Sudden thrombocytopenia followed by hemorrhage
Hepatic and renal toxicity
Nausea, vomiting, and loss of appetite

GLUCOCORTICOIDS

How do glucocorticoids decrease plasma calcium levels? They reduce plasma calcium concentration by decreasing intestinal absorption of calcium and increasing renal excretion of calcium.

What conditions respond best to glucocorticoid (prednisone) therapy? Hypercalcemic states secondary to sarcoidosis and lymphoma. See *Chapter 32—Corticosteroids and Inhibitors* for a more detailed discussion of glucocorticoids.

OTHER AGENTS

What is the role of thiazide diuretics in the treatment of hypercalcemia? Thiazides increase serum calcium levels and therefore are never used in the treatment of hypercalcemia. See *Chapter 23—Diuretics* for further information.

What is the role of loop diuretics in hypercalcemia? These agents, along with aggressive hydration, are often used to reduce serum calcium levels in acute hypercalcemia.

Section VII

Musculoskeletal System

Anti-Inflammatory Drugs and Acetaminophen

What is inflammation?

The reaction of vascularized living tissue to injury

How is inflammation mediated by the body?

Inflammation is initiated and sustained through chemical mediators such as prostaglandins, prostacyclins, bradykinin, histamine, interleukin-1, and leukotrienes.

What exactly are prostaglandins?

Prostaglandins are local mediators (they do not circulate in the blood) that have a variety of physiologic actions. They are a member of a group of compounds known as eicosanoids.

What is an eicosanoid?

An eicosanoid is any biologically active compound derived from arachidonic acid, including prostaglandins, leukotrienes, prostacyclin, and thromboxane.

What is arachidonic acid?

Arachidonic acid is a 20-carbon fatty acid that serves as the precursor for prostaglandin and structurally similar compounds. Arachidonic acid is found in the phospholipids of cell membranes and is liberated by phospholipase A₂.

What are the two major enzymes that use arachidonic acid as a substrate?

Cyclooxygenase and lipoxygenase (Figure 35-1)

Give some examples of prostaglandins and leukotrienes and state their role in inflammation.

Prostaglandin E₂ (PGE₂)—erythema
Prostaglandin I₂ (PGI₂)—vasodilation
Leukotriene C₄—edema
Leukotriene D₄—vasodilation
PGE₂, PGI₂, leukotriene B₄—
pain/tenderness

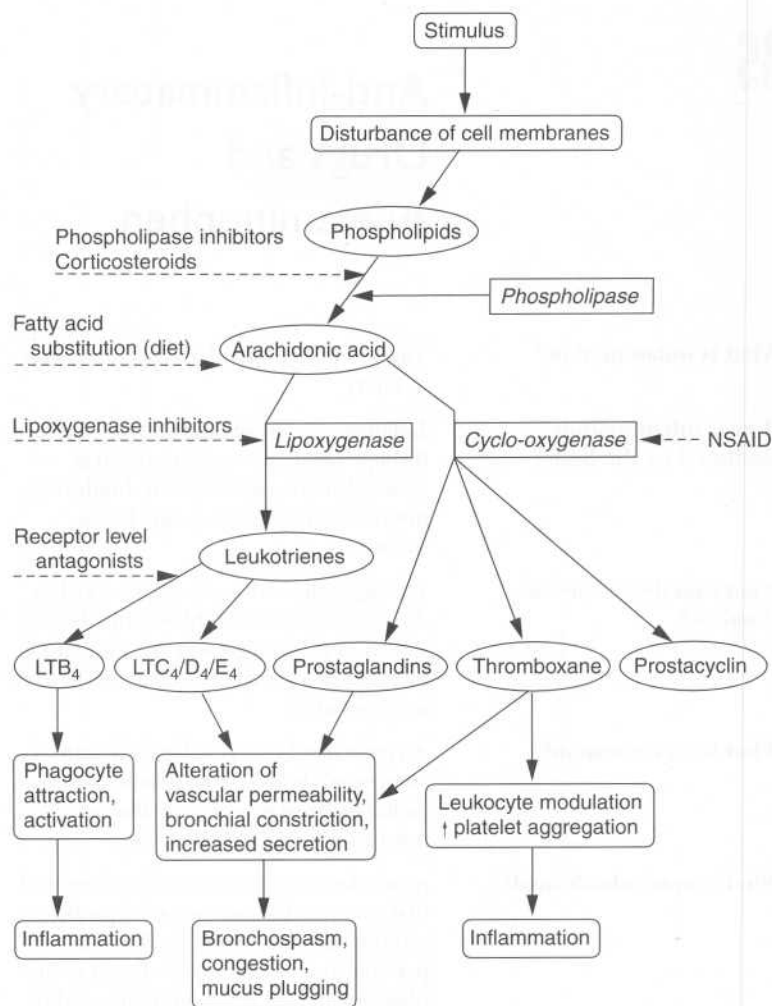


Figure 35–1. Scheme for mediators derived from arachidonic acid and sites of drug action (dashed arrows). (Redrawn from Katzung BG: *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT, Appleton & Lange, 1998, p 582.)

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

What are NSAIDs?

These drugs are a class of chemically dissimilar agents that act by inhibiting the enzyme cyclooxygenase and, subsequently, prostaglandin synthesis.

Name six groups of NSAIDs and give examples of each, including any unique traits they may have.

NSAIDs can be divided into six groups based upon chemical structure:

Salicylates:

Aspirin

Diffunisal—poor antipyretic properties

Salsalate

Pyrazolones:

Phenylbutazone—very toxic; can cause agranulocytosis and aplastic anemia

Indoleacetic Acids:

Indomethacin—used in acute gouty arthritis, ankylosing spondylitis, and to close a patent ductus arteriosus

Sulindac

Etodolac

Ketorolac—excellent analgesic properties; commonly used as an alternative to opioids

Propionic Acids:

Naproxen

Ketoprofen

Ibuprofen

Oxicams:

Piroxicam—long half-life permits once-daily dosing

Fenamates:

Mefenamic acid

Meclofenamic acid

How do NSAIDs work?

By acetylating cyclooxygenase

How does aspirin differ in its action from the other NSAIDs?

Aspirin is unique among NSAIDs by acetylating cyclooxygenase **irreversibly**. All the other NSAIDs inhibit cyclooxygenase in a reversible manner.

What are the four main therapeutic uses of NSAIDs?

1. **Anti-inflammatory**—frequently used for osteoarthritis, gout, rheumatoid arthritis, ankylosing spondylitis, and dysmenorrhea
2. **Analgesia**—alleviates mild to moderate pain

3. **Antipyretic**

4. **Antiplatelet activity**—due to the decreased production of thromboxane. Aspirin's antiplatelet activity lasts 7 days (life span of the platelet); it is often used in the treatment of MI.

How do NSAIDs decrease a patient's fever or pain?

The antipyretic and anti-inflammatory effects of NSAIDs are accomplished by inhibition of prostaglandin synthesis at thermoregulatory centers in the hypothalamus.

How are the NSAIDs metabolized?

They are converted to water-soluble conjugates in the liver and cleared by the kidney. If the hepatic system is overwhelmed, the half-life of the drug will increase dramatically.

Describe the adverse effects of NSAIDs.

Epigastric distress, nausea, and vomiting

—the most common side effects. These effects occur because NSAIDs inhibit prostaglandins that normally stimulate production of the protective mucus of the stomach and small intestine.

Coagulation disorders—Aspirin should be stopped at least 1 week before surgery.

Metabolic abnormalities—At moderate levels of intoxication, NSAIDs uncouple oxidative phosphorylation, which results in energy being wasted as heat. This is clinically manifested as fever.

Hypersensitivity—Approximately 15% of patients will experience urticaria or bronchoconstriction.

Reye's syndrome risk—Aspirin, when given to children who have a fever secondary to a viral infection, has been associated with an increased incidence of Reye's syndrome, which is characterized by cerebral edema and hepatitis.

The newer NSAIDs have a lower incidence of gastric disturbances but a higher incidence of renal damage.

What is salicylism?

When plasma levels of NSAIDs go beyond maximum therapeutic range, patients develop salicylate toxicity, or salicylism. The features of salicylism can vary with plasma levels:

Mild:

Tinnitus
Vertigo
Respiratory stimulation

Severe:

Coma
Metabolic acidosis
Delirium
Hallucinations
Respiratory and renal depression
Refer to Figure 35–2.

What is the treatment for salicylate toxicity?

Maintaining respiration and circulation, minimizing drug absorption (via gastric lavage), and maximizing elimination (alkalinizing the urine enhances elimination).

What other agents are used to treat inflammation?

Corticosteroids, such as prednisone. These agents are discussed further in *Chapter 32—Corticosteroids and Inhibitors*.

SLOW-ACTING ANTIRHEUMATIC DRUGS (SARDs)**Name four slow-acting antirheumatic drugs.**

1. Methotrexate
2. Gold salts
3. Penicillamine
4. Hydroxychloroquine

Why are these drugs considered slow-acting?

It may take several months for the benefits to become apparent. The drugs may, however, induce a remission of the rheumatic disease.

What are the clinical indications for SARDs?

They are used in patients with rheumatoid arthritis who do not respond to other agents. Remember, **SARDs are not first-line agents**.

How does methotrexate work?

Methotrexate acts by reducing the number of cells available to sustain the inflammatory response.

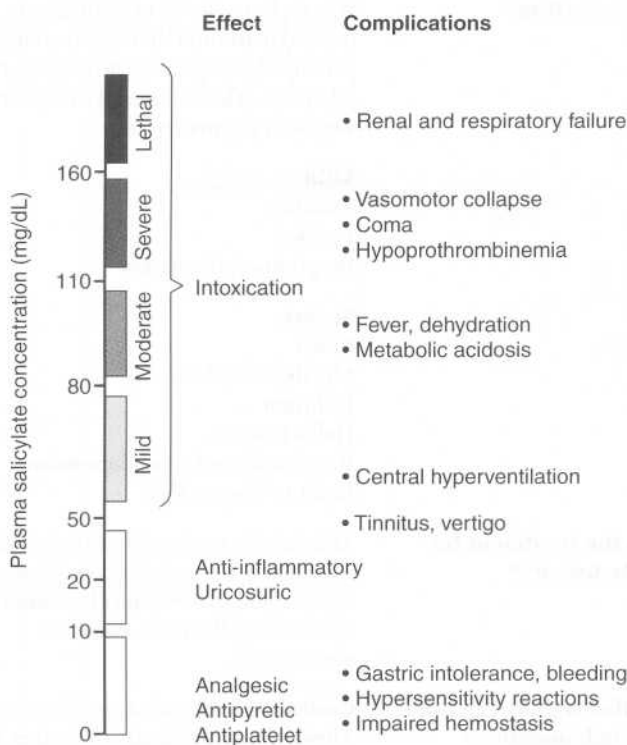


Figure 35-2. Approximate relationships of plasma salicylate levels to pharmacodynamics, and complications. (Modified and reproduced with permission from Hollander J, McCarty D Jr: *Arthritis and Allied Conditions*. Philadelphia, Lea & Febiger, 1972.)

What is the mechanism of action of gold salts?

These drugs alter the activity of macrophages.

How does penicillamine work?

This drug slows the progress of bone destruction, but its mechanism of action is unknown.

What is the mechanism of action for hydroxychloroquine?

It may interfere with the activity of T lymphocytes and trap free radicals, as well as interfere with DNA/RNA synthesis.

What is the toxicity of SARDs?

These agents have the following very serious potential side effects:
Methotrexate—causes bone marrow suppression and cirrhosis of the liver

Gold salt compounds—commonly cause a dermatitis (especially of the mouth), but can also cause agranulocytosis and aplastic anemia.

Penicillamine—causes aplastic anemia and renal damage.

Hydroxychloroquine—can cause dermatitis, retinal destruction, and bone marrow depression.

Careful supervision of patients taking SARDs is essential.

ACETAMINOPHEN (TYLENOL) AND PHENACETIN

What is acetaminophen?

Acetaminophen is an over-the-counter weak anti-inflammatory analgesic and antipyretic medication that is routinely administered.

What is phenacetin?

Phenacetin is a prodrug that is metabolized to acetaminophen. It is not available in the United States because of serious side effects.

How does acetaminophen work?

This drug acts by inhibiting prostaglandin synthesis in the central nervous system. It has much less of an effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory effects.

What are the general clinical indications for acetaminophen?

Fever and mild-to-moderate pain

What are other, more specific clinical uses for this drug?

Patients who have peptic ulcer disease or hemophilia tolerate acetaminophen better than NSAIDs. Acetaminophen is also indicated for children who have viral infections, because aspirin increases the risk of Reye's syndrome.

How does acetaminophen affect platelets?

Acetaminophen does not affect platelet function, nor does it have any effect on blood clotting time.

Can acetaminophen be administered to gout patients who are taking probenecid?

Yes. Unlike aspirin, acetaminophen does not antagonize the uricosuric agent probenecid.

What is the metabolism of this drug?

Acetaminophen is metabolized in the liver by the cytochrome P-450 system.

What are the important side effects of acetaminophen?

Acetaminophen has a negligible side-effect profile, except for hepatotoxicity, which is the main concern when overdoses occur.

Why does acetaminophen cause hepatotoxicity?

Toxic doses of acetaminophen surpass the liver's supply of glutathione, a compound that normally binds to and inactivates dangerous metabolites of acetaminophen such as *N*-acetyl-*p*-benzoquinone. Without glutathione, these metabolites will bind to hepatic proteins and cause necrosis.

What can be given to counteract the effects of acetaminophen?

N-acetylcysteine (Mucomyst) can be administered. It has a sulfhydryl group similar to glutathione and therefore acts as a temporary substitute to bind any free toxic metabolites.

36

Drugs Used to Treat Gout

What is gout?

Gout is a familial metabolic disease associated with high blood levels of uric acid (hyperuricemia). The disease is characterized by attacks of arthritis and urinary calculi, which are caused by deposits of sodium urate crystals in joints, cartilage, and the kidneys (Figure 36-1).

What are the common clinical signs and symptoms of gout?

During the initial attacks, the usual presentation is sudden pain in a single joint, most often the metatarsophalangeal joint of a great toe.

Whom does gout usually affect?

Men. Onset is usually in the 40's.

What is uric acid?

Uric acid is the end product of **purine metabolism** and is excreted mainly via the kidney (Figure 36-2).

What is the definition of hyperuricemia?

Hyperuricemia is usually defined as a serum concentration of uric acid greater than 7 mg/dL. It is important to note that hyperuricemia is not always associated with gout; however, gout is always preceded by hyperuricemia.

What are the causes of hyperuricemia?

Idiopathic enzyme defects in purine metabolism—90% of cases (this is known as *primary gout*)

Disease states associated with rapid production and destruction of cells—myeloproliferative disorders and malignancies, especially those treated with chemotherapy or radiation (this is known as *secondary gout*)

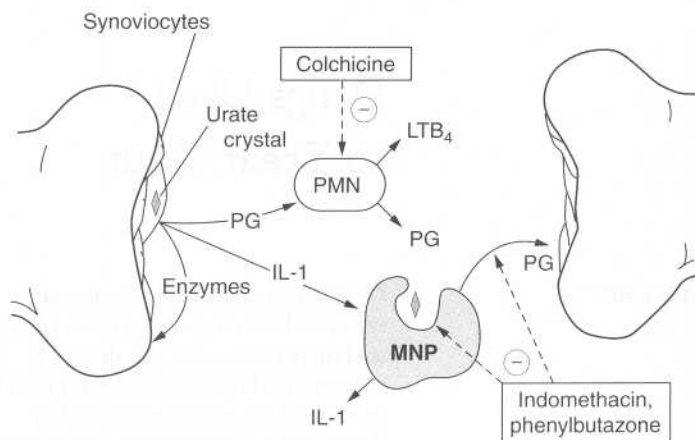


Figure 36-1. Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP)[macrophages]. Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear leukocyte and macrophage release of inflammatory mediators. PG = prostaglandin; IL-1 = interleukin-1; LTB₄ = leukotriene B₄. (Redrawn from Katzung BG: *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT, Appleton & Lange, 1998, p 596.)

Weakly acidic drugs such as clofibrate, thiazides, and salicylates can cause decreased renal excretion of uric acid. **Other causes** include excessive alcohol intake, kidney disease, high purine diets, starvation, and obesity.

How is gout treated?

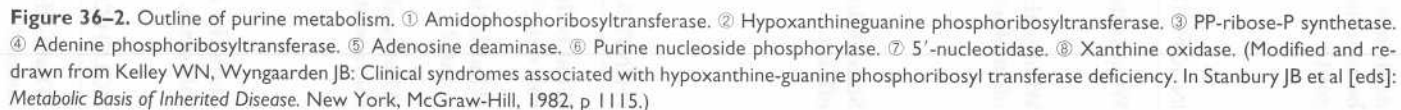
It depends on whether the patient is suffering from an acute attack or a chronic case. The general treatment strategy is as follows:

- Reduce inflammation (via NSAIDs)
- Facilitate the excretion of uric acid (via uricosuric agents)
- Decrease the production of purines (via allopurinol)

ACUTE GOUT

What pharmacologic agents are available for treating an acute attack of gout?

Indomethacin
Phenylbutazone
Colchicine



Aspirin is an NSAID—can it be used in the treatment of gout?

No! Aspirin, because it is a salicylate, inhibits uric acid secretion into the renal tubules and therefore is contraindicated in the treatment of gout. It also antagonizes the effects of probenecid and sulfipyrazone.

INDOMETHACIN (INDOCIN)

What is its therapeutic use?

It is the drug of choice to treat **acute attacks** of gout.

What is this drug's mechanism of action?

It reversibly inhibits cyclooxygenase. Consequently, the production of prostaglandins and thromboxane, which are responsible for inflammation, is reduced.

State indomethacin's adverse effects.

Headache, vertigo
Abdominal distress
Renal toxicity
Hypersensitivity reactions
See *Chapter 35—Anti-inflammatory Drugs and Acetaminophen* for a more detailed discussion of NSAIDs.

PHENYLBUTAZONE (AZOLID)

What is the classification of this drug?

Phenylbutazone, like indomethacin, is an NSAID.

What is the mechanism of action?

Same as that of indomethacin

What is phenylbutazone's therapeutic use?

Phenylbutazone was used more often in the past for treating acute cases of gout. However, because it has a high incidence of side effects, it is not used frequently today.

State the adverse effects of this drug.

Vomiting
Skin rash
Aplastic anemia and agranulocytosis

COLCHICINE

What is the mechanism of action?

Colchicine reduces the inflammatory response by binding to microtubular

	protein, thus inhibiting neutrophil migration and phagocytic activity. (Neutrophils are largely responsible for the inflammation and pain associated with gout.) Colchicine also decreases leukotriene B ₄ formation.
Does colchicine affect the production or excretion of uric acid?	No
What is this drug's route of administration?	Oral or IV
State colchicine's therapeutic use.	Colchicine is used to treat both acute and chronic gout. A dramatic response to colchicine makes the diagnosis of gout likely.
What are the adverse effects of colchicine?	Most common effects—GI distress (vomiting, diarrhea, abdominal pain) Acute poisoning after large doses can lead to nephrotoxicity, bloody diarrhea, and shock. With chronic use—possible agranulocytosis, alopecia, and aplastic anemia Myopathy has been reported (rare).
What are the relative contraindications to colchicine use?	Colchicine is contraindicated in patients who have GI disease, hepatitis, or renal disease.

CHRONIC GOUT

What pharmacologic options are available for a chronic case of gout?	Colchicine (<i>see above</i>) Uricosuric agents—probenecid and sulfinpyrazone Allopurinol
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URICOSURIC AGENTS

What are they?	Weak organic acids that interfere with the renal processing of uric acid
Give two examples.	1. Probenecid (Benemid) 2. Sulfinpyrazone (Anturane)

What is the mechanism of action of these drugs?

The actions of uricosuric agents are dependent upon their serum concentrations:

At low concentrations they reduce the renal excretion of uric acid by inhibiting uric acid secretion into the renal tubules.

At therapeutic concentrations they increase uric acid excretion by inhibiting uric acid reabsorption in the proximal tubule.

It is important to remember that low doses of uricosuric agents and salicylates such as aspirin actually *increase* serum uric acid concentration.

What is the route of administration for these drugs?

Oral

What is their therapeutic use?

Treatment of chronic gout (to avoid attacks) and severe hyperuricemia. These drugs are *not* indicated in the treatment of acute attacks of gout.

What are the adverse effects of probenecid and sulfipyrazone?

They can precipitate an acute attack of gouty arthritis in the early stages of treatment.

Gastrointestinal distress

Allergic dermatitis

ALLOPURINOL (LOPURIN)

What is it?

Allopurinol is an isomer of hypoxanthine.

What is xanthine oxidase?

Xanthine oxidase is the enzyme that catalyzes the terminal steps of uric acid synthesis. It converts hypoxanthine to xanthine and xanthine to uric acid (see Figure 36-2).

How does allopurinol work?

Allopurinol and its metabolite **alloxanthine** competitively inhibit the enzyme xanthine oxidase.

What are the therapeutic uses of allopurinol?

Treatment of chronic gout

Treatment of the hyperuricemia associated with Lesch-Nyhan syndrome, hematologic disorders (polycythemia vera, myeloid metaplasia) or antineoplastic therapy
prevention of renal calculi

State the route of administration for allopurinol.

Oral

Can you combine allopurinol with other antigout drugs?

Yes. Because urate-lowering drugs can initially precipitate an acute gout attack, colchicine is often given concurrently with allopurinol or the uricosuric agents.

What are this drug's adverse effects?

Allopurinol is usually well tolerated but can cause hypersensitivity reactions (allergic dermatitis, fever) and gastrointestinal distress (diarrhea, abdominal pain). Attacks of acute gout may occur during initial months of therapy.

Are allopurinol, probenecid, and sulfinpyrazone indicated in the treatment of acute attacks?

No. These drugs are usually begun once the acute attack is under control. Remember to use indomethacin and colchicine for acute attacks.

Autocoids and Autocoid Antagonists

What is an autocoid?


This word is derived from the Greek words *autos* (self) and *akos* (medicinal agent or remedy)—hence **self agent**. Autocoids can be thought of as locally acting hormones that involve a wide variety of pharmacological activities. These agents are not secreted into the systemic blood-stream as are true hormones.

Name 2 of the principle autocoids within the body.

1. Serotonin
2. Histamine

Although ergot alkaloids are not truly autocoids, they are discussed in this chapter because of their important actions on smooth muscle.

Are these the only autocoids of the body?

No. Several other compounds, such as bradykinins and prostaglandins, are included in this group, but histamine and serotonin are the most likely to be tested on the USMLE Step 1 exam .

SEROTONIN AND SEROTONIN ANTAGONISTS

What is serotonin?

Serotonin (5-hydroxytryptamine, or 5-HT) is an indole ethylamine found in both plant and animal tissues.

What is serotonin derived from?

The amino acid L-Tryptophan

Where is most of the serotonin in the body found?

The enterochromaffin cells of the GI tract contain approximately 90%, the CNS contains most of the remaining 10%.

How does serotonin exert its actions?

Through seven major 5-HT cell membrane receptor subtypes

How is serotonin metabolized?	By monoamine oxidase
What are this agent's physiologic actions?	<p>Neurotransmission</p> <p>Regulation of the pituitary gland</p> <p>Vasoconstriction (except for skeletal muscle and heart, where it causes vasodilation)</p> <p>Contraction of GI smooth muscle</p> <p>Stimulation of pain receptors</p> <p>Precursor to melatonin</p>
Name a serotonin agonist.	Sumatriptan
What is this agent used for?	To treat migraine headaches
What are the adverse effects of sumatriptan?	Dizziness and muscle weakness and neck pain
Name three serotonin inhibitors and describe their clinical uses.	<p>Ketanserin—lowers blood pressure</p> <p>Ondansetron—treatment of nausea and vomiting associated with surgery and chemotherapy</p> <p>Cyproheptadine—treatment of smooth muscle constriction in carcinoid tumor</p>
Are these drugs selective serotonin inhibitors?	No. They block 5-HT receptors, but they also inhibit H_1 and α receptors.

HISTAMINE AND HISTAMINE BLOCKERS

What is the mechanism of action?	Histamine formed from the amino acid histidine exerts its effects by binding to H_1 and H_2 receptors, which are located on cell surfaces and mediate a variety of physiological responses.
Where is histamine found within the body?	Within granules of mast cells and basophils
What is its physiologic role?	<p>Histamine when released from mast cells and basophils, causes</p> <p>Constriction of bronchioles (H_1 receptors)</p> <p>Constriction of intestinal smooth muscle (H_1 receptor)</p> <p>Stimulates sensory nerve endings mediating pain and (H_1 receptors) itching</p> <p>Lowers blood pressure (H_2 receptors)</p> <p>Stimulates gastric HCL secretion (H_2 receptors)</p>

	Increases permeability of skin capillaries (H ₂ receptors)
What are the clinical uses of histamine?	Histamine itself is of no use clinically. However, histamine blockers are very important.
Name some H ₁ -receptor blockers and their clinical uses.	Diphenhydramine —allergic reactions, motion sickness Hydroxyzine —allergic reactions Promethazine —motion sickness
Name a few H ₂ -receptor blockers.	Cimetidine Ranitidine Famotidine These drugs are discussed further in <i>Chapter 38—Drugs Used to Treat Gastrointestinal Disorders</i> .

ERGOT ALKALOIDS

What are ergot alkaloids?	A group of compounds produced by the fungus <i>Claviceps purpurea</i> .
What is their mechanism of action?	The ergot alkaloids interact with adreno-receptors, 5-HT receptors, and dopamine receptors.
What are their physiologic actions?	Hallucinations and psychoses at high doses Vasoconstriction Stimulation of uterine muscle
Give some examples of ergot alkaloids.	Bromocriptine Ergonovine Ergotamine
What are these agents' clinical uses?	Migraine—ergotamine diminishes cerebral vascular pulsations. Hyperprolactinemia—bromocriptine Postpartum hemorrhage—ergonovine and ergotamine
What are the adverse effects?	Prolonged vasoconstriction—may result in gangrene (Nitroprusside can be administered to treat ergotamine-induced vasoconstriction.) Diarrhea Nausea, vomiting Unwanted uterine contraction CNS psychosis

Section VIII

Gastrointestinal System

38

Drugs Used to Treat Gastrointestinal Disorders

DRUGS USED TO TREAT ACID-PEPTIC DISEASE

What is acid-peptic disease?	Acid-peptic disease includes peptic ulcer (gastric and duodenal), gastroesophageal reflux, and pathologic hypersecretory states such as Zollinger-Ellison syndrome.
What is the pathogenesis of peptic ulcer disease?	Factors that play an important role include: Gastric acid and pepsin secretion Decreased mucosal resistance to acid <i>Helicobacter pylori</i>
What are the therapeutic options for treating peptic ulcer disease?	Antacids—neutralize gastric acid H ₂ -receptor blockers and proton pump inhibitors—reduce gastric acid secretion Mucosal protective agents—enhance mucosal defenses

ANTACIDS

What are gastric antacids?	Gastric antacids are weak bases that react with gastric hydrochloric acid to form a salt and water. The net result is increased gastric pH.
Name the active ingredients of antacids.	Calcium carbonate (Tums) Aluminum hydroxide Magnesium hydroxide (Milk of Magnesia)
List the major side effects of each.	Calcium carbonate's side effects include nephrolithiasis and fecal compaction .

Aluminum hydroxide reacts with hydrochloric acid to form aluminum chloride, which is insoluble and causes **constipation**.

Magnesium hydroxide produces magnesium salts which, because they are poorly absorbed, cause the diarrhea commonly associated with this compound.

H₂-RECEPTOR BLOCKERS

What factors control gastric acid secretion?

Three principal agonists control gastric acid secretion: histamine, acetylcholine, and gastrin.

What biochemical mechanism do these three factors share?

The final common pathway of these compounds is through activation of the H⁺/K⁺ ATPase proton pump (Figure 38-1).

How effective are H₂-receptor blockers in reducing gastric acid?

H₂-receptor blockers are capable of reducing more than 90% of basal secretions of gastric acid after a single dose.

Do these agents have additional therapeutic value?

They have been shown to be effective in promoting healing of duodenal and gastric ulcer as well as preventing their recurrence.

Name four H₂-receptor blockers.

1. Cimetidine (Tagamet)
2. Ranitidine (Zantac)
3. Famotidine (Pepcid)
4. Nizatidine (Axid)

Is there any therapeutic difference among the H₂-receptor blockers?

No. All of these drugs are equally effective in treating acid-peptic disease.

How can H₂ blockers be given?

IV or orally

What are the side effects of H₂-receptor blockers?

The longest clinical experience is with cimetidine, but the other drugs associated with this class are similar. Prolonged therapy with cimetidine is associated with: Confusional states
Nausea

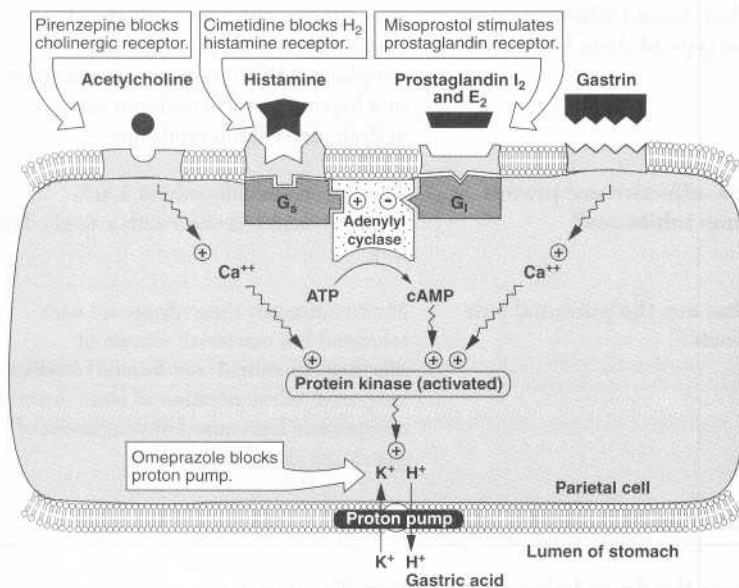


Figure 38–1. Effects of acetylcholine, histamine, prostaglandin I_2 and E_2 , and gastrin on gastric acid secretion by the parietal cells of the stomach. G_s and G_i are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenyl cyclase. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 237.)

Headaches
 Reversible gynecomastia
 Elevated serum prolactin levels (results in galactorrhea)
 Altered estrogen metabolism in men
 Inhibition of hepatic (P_{450}) metabolism

PROTON PUMP INHIBITORS

Name the proton pump inhibitors.

Omeprazole (Prilosec)—prototype
 Lansoprazole (Prevacid)

Explain how these drugs work.

Omeprazole and lansoprazole are a substituted benzimidazoles that become active in an acidic environment and irreversibly inhibit the H^+/K^+ ATPase proton pump on the luminal surface of parietal cells.

When would administering this type of drug be useful?

For patients with reflux, duodenal or gastric ulcer, multiple endocrine neoplasia (MEN), systemic mastocytosis, or a hypersecretory condition such as Zollinger-Ellison syndrome

How effective are proton pump inhibitors?

They can essentially inhibit 100% of gastric acid secretion with a single daily dose.

What are the potential side effects?

Most commonly these drugs are well tolerated but can cause nausea or diarrhea. In animal (*not human*) studies, long-term administration of large doses of omeprazole has caused development of gastric carcinoid tumors.

MUCOSAL PROTECTIVE AGENTS

Name the drugs belonging to this class.

Sucralfate (Carafate)
Bismuth
Misoprostol (Cytotec)

Sucralfate (Carafate)

What is sucralfate?

Sucralfate is a sulfated disaccharide developed for use in treating peptic ulcer disease.

What is its major mechanism of action?

Polymerization and selective binding to necrotic ulcer tissue, where it acts as a barrier to acid, pepsin, and bile.

What other actions are possible?

Sucralfate may also directly adsorb bile salts and may stimulate endogenous prostaglandin synthesis.

Can sucralfate be taken with H₂-receptor blockers or proton pump inhibitors?

No. Sucralfate requires an acid pH to be activated and should not be administered simultaneously with either H₂-receptor blockers or proton pump inhibitors.

Bismuth

How does bismuth work?

Like sucralfate, bismuth compounds appear to work by selectively binding to an ulcer, coating it and protecting it from acid and pepsin.

What other therapeutic actions are possible? Bismuth compounds may have some antimicrobial activity against *H. pylori*. When bismuth compounds are combined with antimicrobials (metronidazole and tetracycline), ulcer healing rates of up to 98% have been reported.

Misoprostol

How does this drug work? Misoprostol is a prostaglandin E₁ analog that may stimulate gastric secretion of mucus and other protective factors.

What are the clinical indications for administering misoprostol? Peptic and duodenal ulcers, especially if caused by long-term NSAID use

What are its major side effects? Diarrhea and unwanted uterine contractions

PROKINETIC AGENTS

What conditions can be treated with prokinetic agents? Gastroesophageal reflux and gastroparesis

Name two drugs in this class.

1. Cisapride (Propulsid)
2. Metoclopramide (Reglan)

Cisapride

How does cisapride work? It stimulates the release of acetylcholine at the myenteric plexus, which results in increased esophageal sphincter tone and therefore decreased reflux.

What are its toxicities? Diarrhea

Metoclopramide

Which receptors does metoclopramide stimulate? 5-HT₃ and D₂ receptors in gastric smooth muscle, which results in acceleration of GI emptying

What types of adverse effects can be seen with this drug? Extrapyramidal side effects (parkinsonism and tardive dyskinesia)
Diarrhea
Drowsiness

ANTIEMETIC DRUGS

State the major categories of antiemetics and give an example of each.

H₁ antihistamines—diphenhydramine
 Phenothiazines—prochlorperazine
 (Compazine)
 Marijuana—dronabinol (Marinol)
 5-HT₃ inhibitors—ondansetron (Zofran)

What are the clinical indications for these drugs?

Any condition that is inducing emesis, such as chemotherapy or GI infection
 Antiemetic drugs are discussed in more detail in other chapters (see index).

LAXATIVES

How are laxatives classified?

These drugs are generally classified by simplified mechanism of action, that is, as stimulants, bulking agents, and stool softeners.

STIMULANTS

Give some examples of stimulant laxatives.

Castor oil
 Senna (Senokot)
 Phenolphthalein (Ex-Lax)
 Bisacodyl (Dulcolax)

What are the side effects of stimulant laxatives?

Chronic stimulation of the colon can lead to chronic colonic distention and thus perpetuation of the perceived need for laxatives.

BULKING AGENTS

Name some members of this group.

These agents, which are usually insoluble during the digestive process, include:
 Hydrophilic colloids (from indigestible parts of fruits and vegetables)
 Agar
 Methylcellulose
 Bran
 Saline cathartics (magnesium citrate and magnesium hydroxide)
 Lactulose
 Sorbitol

How do these agents work?

They are nonabsorbable agents that increase water retention and stool bulk, which distends the bowel and stimulates peristalsis.

STOOL SOFTENERS

How do these agents work?

By emulsifying stool, these agents soften it and make its passage easier.

Name some stool softeners.

Examples include mineral oil, glycerin suppositories, and detergents such as dioctyl sodium sulfosuccinate (docusate).

Section IX

Immune System

39

Antineoplastic Drugs

What is the definition of a neoplasm?

The word *neoplasm* simply refers to a collection of abnormally proliferating cells. *Benign neoplasms* do not invade surrounding tissue. *Malignant neoplasms* can invade and metastasize to all parts of the body and are usually fatal.

Name the five stages of the cell cycle.

1. G_1 —synthesis of components needed for DNA synthesis
 2. S—DNA synthesis
 3. G_2 —growth and replication of cytoplasmic constituents
 4. M—mitosis
 5. G_0 —resting phase
- See Figure 39-1.

What is the significance of a cell cycle-specific (CCS) antineoplastic agent?

Cell cycle-specific means that the drug will primarily affect the cells that are actively replicating or cycling through G_1 to M (Figure 39-1). Cell cycle-specific drugs include:

- Antimetabolites
- Plant alkaloids
- Bleomycin
- Steroid hormones

What are cell cycle-nonspecific (CCNS) drugs?

CCNS drugs kill cells whether they are cycling or resting (G_0). They are more toxic, but are more effective for slow-growing tumors. Cell cycle-nonspecific agents include alkylating agents and antibiotics.

What are the options for treating cancer in addition to chemotherapy?

Surgery, immunotherapy, and radiotherapy are often used initially to reduce the neoplastic cell burden (debulking) this is often followed by chemotherapy

State five classes of antineoplastic agents and give examples of each.

1. **Alkylating agents**—mechlorethamine (Mustargen), cyclophosphamide (Cytoxan), melphalan (Alkeran),

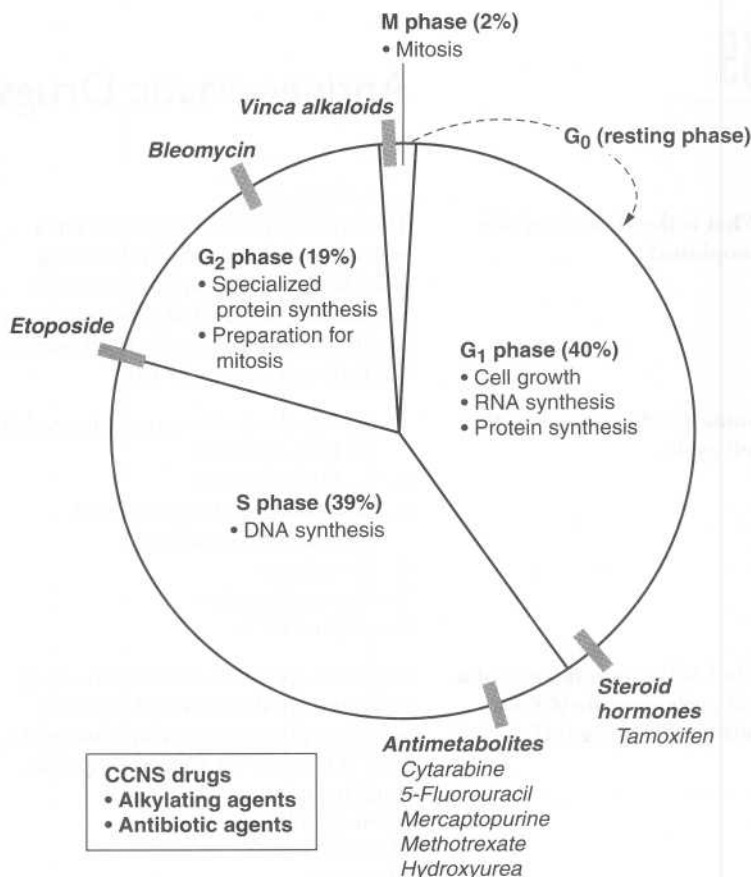


Figure 39-1. Cell cycle-specific antineoplastic drugs. The percentages indicate the approximate percentage of time spent in each phase by a typical malignant cell. The duration of the G₁ phase, however, can vary markedly.

lomustine (CeeNu), streptozocin (Zanosar), cisplatin (Platinol), busulfan (Myleran), dacarbazine (DTIC), procarbazine (matulane)

2. **Antibiotics**—daunorubicin (Cosmegen), doxorubicin (Adriamycin), daunorubicin (Cerubidine), bleomycin (Blenoxane), mitomycin (Mutamycin), plicamycin (Mithracin)
3. **Antimetabolites**—methotrexate (Folex), 6-mercaptopurine

(Purinethol), cytarabine (Cytosar-U), 5-fluorouracil (Adrucil), hydroxyurea (Hydrea)

4. **Hormones and related agents**—flutamide (Eulexin), tamoxifen (Nolvadex), leuprolide (Lupron), glucocorticoids
5. **Plant alkaloids**—vinblastine (Velban), vincristine (Oncovin), etoposide (VePesid), paclitaxel (Taxol) (see Fig 39–2)

How does resistance develop to chemotherapeutic drugs?

Neoplastic cells can defend themselves in several ways including:
Increased DNA repair
Changes in target enzymes
Drug inactivation
Decreased drug accumulation
Alternative metabolic pathways

ALKYLATING AGENTS

What are alkylating agents?

A group of cell cycle-nonspecific compounds that transfer an alkyl group, usually to the 7 nitrogen atom of guanine residues in one or both strands of DNA

What are the major classes of alkylating agents?

Nitrogen mustards and nitrosoureas

NITROGEN MUSTARDS

Mechlorethamine (Mustargen)

What is its mechanism of action?

Mechlorethamine binds with the N7 atom of guanine in DNA. This, in turn, results in cross-linking, strand breaks, and miscoding mutations.

How is this drug used clinically?

As a component of MOPP (mechlorethamine, Oncovin [vincristine], procarbazine, and prednisone) therapy in Hodgkin's disease

What is its route of administration?

IV

Are there adverse effects?

Yes—severe bone marrow suppression, severe nausea and vomiting, and lacrimation

Cyclophosphamide (Cytosan)**What is the mechanism of action?**

Cyclophosphamide is metabolized in the P_{450} system. The metabolite of this drug, called phosphoramidate mustard, cross-links DNA and RNA strands.

How is cyclophosphamide used clinically?

For treating ovarian and breast carcinoma, Hodgkin's and non-Hodgkin's lymphoma, and all of the leukemias. It is also used as an immunosuppressive agent in transplantation.

What is the preferred route of administration?

Oral

Describe the adverse effects.

Hemorrhagic cystitis
GI effects (nausea and vomiting)
Bone marrow suppression
Skin pigmentation
Severe alopecia
Gonadal suppression

Melphalan (Alkeran)**Explain melphalan's mechanism of action.**

This drug is a phenylalanine derivative of nitrogen mustard that cross-links strands of DNA and RNA.

How is melphalan used clinically?

For treating ovarian carcinoma and multiple myeloma

What are the adverse effects?

Bone marrow suppression, leukopenia, and thrombocytopenia

NITROSOUREAS**Lomustine (CeeNu) and Carmustine (BiCNU)****How do these drugs work?**

Lomustine and carmustine alkylate DNA, which results in strand breakage and inhibition of protein synthesis.

Describe the solubility of these agents.

Lomustine and carmustine are very lipophilic molecules, which partially accounts for their CNS activity.

What are the clinical uses?	Treatment of brain tumors, melanoma, and GI cancers
State the adverse effects.	Both drugs cause delayed bone marrow depression (usually 4–6 weeks after onset of use), GI effects (nausea and vomiting), and flushing of the skin and conjunctiva. High doses can cause pulmonary fibrosis and renal failure.
Streptozocin (Zanosar)	
State the mechanism of action.	Streptozocin is an alkylating agent that inhibits DNA synthesis by cross-linking strands of DNA
What is the clinical use?	Treatment of pancreatic insulinoma
Describe the adverse effects.	GI effects (nausea and vomiting) and renal failure

MISCELLANEOUS ALKYLATING AGENTS

Cisplatin (Platinol)

How does it work?	Cisplatin is a member of the platinum coordination complex, which forms cross-links with DNA and inhibits DNA synthesis.
When do you use cisplatin?	For treating testicular, bladder, lung, and ovarian carcinomas
What are the adverse effects?	Nephrotoxicity—the number-one toxicity, which can be limited with aggressive hydration and mannitol Ototoxicity Paresthesias

Carboplatin (Paraplatin)

Describe the mechanism of action.	Same as cisplatin
What is its clinical use?	Treatment of ovarian carcinomas
Are there adverse effects?	Yes—bone marrow suppression and anemia

Busulfan (Myleran)

State the mechanism of action.	This drug cross-links strands of DNA.
How is it used clinically?	Busulfan is effective for treating chronic myelocytic leukemia (CML).
What are the adverse effects?	Bone marrow suppression Hyperuricemia Amenorrhea Impotence

Dacarbazine (DTIC)

Describe the mechanism of action.	This drug inhibits DNA and RNA synthesis via formation of toxic methyl carbonium ions.
What is the clinical use?	Treatment of Hodgkin's lymphoma and melanoma
State the adverse effects.	GI effects (nausea and vomiting), hepatotoxicity, and bone marrow suppression

Procarbazine (Matulane)

How does this drug work?	Procarbazine forms hydrogen peroxide, which in turn creates free radicals that cause DNA strand lysis. It also inhibits synthesis of RNA and protein.
What is the clinical use?	Treatment of Hodgkin's disease
List the adverse effects.	Myelosuppression and gastrointestinal irritation. Also, procarbazine is leukemogenic and teratogenic.

ANTIBIOTICS

Where do these antineoplastic antibiotics originate?	From various strains of the soil fungus <i>Streptomyces</i>
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DACTINOMYCIN (COSMEGEN)

How does it work?	Dactinomycin binds to the double helix of DNA and forms a dactinomycin-DNA complex, which in turn inhibits the actions of DNA-dependent RNA polymerase. The drug may also cause DNA single-strand breaks.
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When do you use dactinomycin?	To treat Wilms' tumor and rhabdomyosarcoma in children. It is also used for choriocarcinoma and Kaposi's sarcoma.
What is the route of administration?	IV
List the adverse effects.	Bone marrow depression and GI distress are usually the dose-limiting toxicities. Skin abnormalities associated with prior radiation therapy may occur.

DOXORUBICIN (ADRIAMYCIN) AND DAUNORUBICIN (CERUBIDINE)

How do these two drugs work?	They are anthracycline antibiotics whose antitumor activity may result from several mechanisms: —They bind to adjacent base pairs along the sugar-phosphate backbone of DNA, thus blocking DNA and RNA synthesis. —They disrupt cell membranes. —They generate oxygen radicals, which cause single-strand breaks in DNA.
What are the clinical indications?	Doxorubicin is used to treat acute leukemias and cancers of the breast, endometrium, ovary, thyroid, and lung. Daunorubicin is also used for treating acute leukemias (AML and ALL).
How are these two drugs administered?	Both must be administered intravenously.
Are there adverse effects?	Yes. Irreversible cardiotoxicity is the most important (common board question); this effect may be a result of the oxygen-free radical production. These drugs can also cause bone marrow depression, alopecia, GI distress, and stomatitis.

BLEOMYCIN (BLENOXANE)

How does it work?	Bleomycin combines with Fe^{2+} to form a complex that reacts with oxygen to produce free radicals, which cause strand scission and DNA fragmentation.
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What are the clinical uses?

Bleomycin is a component of the regimens for testicular carcinoma and Hodgkin's disease.

How is bleomycin administered?

It can be given by intramuscular, intravenous, subcutaneous, or intracavitary routes.

Describe the adverse effects.

Pulmonary toxicity (☞ board question)

Fever and chills

Mucocutaneous toxicity

Hypersensitivity reactions (anaphylaxis)

MITOMYCIN (MUTAMYCIN)

Describe the mechanism of action.

Mitomycin is metabolically reduced to an alkylating agent, which inhibits DNA synthesis.

When is mitomycin used clinically?

Carcinoma of the cervix, lung, bladder, and colon

What are the adverse effects?

GI effects (nausea, vomiting, loss of appetite) and severe bone marrow suppression

PLICAMYCIN (MITHRACIN)

What is plicamycin's mechanism of action?

Plicamycin intercalates DNA base pairs in a manner similar to doxorubicin and inhibits RNA synthesis.

How is it administered?

Intravenously

What are the clinical indication for using plicamycin?

It is used in treating testicular cancer, but its use is limited because of severe toxicity. It is also used to reduce hypercalcemia of malignancy.

What are its toxicities?

Severe bone marrow suppression

Bleeding disorders

Hepatic and renal toxicity

ANTIMETABOLITES**METHOTREXATE (FOLEX)****How does it work?**

Methotrexate is a folic acid antagonist that prevents the conversion of dihydrofolate to tetrahydrofolate by inhibiting the action of dihydrofolate reductase. This results in decreased synthesis of thymidylate, amino acids, and purine nucleotides, which make up DNA and RNA.

Describe methotrexate's clinical uses.

Methotrexate is used in treating the following conditions:

Choriocarcinoma

Lung cancer

Acute lymphocytic leukemia (ALL)

Non-Hodgkin's lymphoma

Breast cancer

Methotrexate has a number of other clinical uses, including the treatment of psoriasis and rheumatoid arthritis.

What are the adverse effects of methotrexate?

Bone marrow suppression

GI hemorrhagic enteritis

Neurotoxicity (seizures, encephalopathy)

Hepatotoxicity

What is the "leucovorin rescue"?

Toxic effects upon normal cells can be minimized with the administration of leucovorin (folinic acid), which is preferentially absorbed by normal cells but not by neoplastic cells.

6-MERCAPTOPURINE (PURINETHOL)**Describe how this drug works.**

6-Mercaptopurine is a purine analog that enters target cells and then is converted to 6-thioinosinic acid by hypoxanthine guanine phosphoribosyl transferase (HGPRT). This active compound then inhibits a number of enzymes in purine interconversion.

State the clinical uses.

Treatment of ALL and AML

What is the mode of administration?

Oral

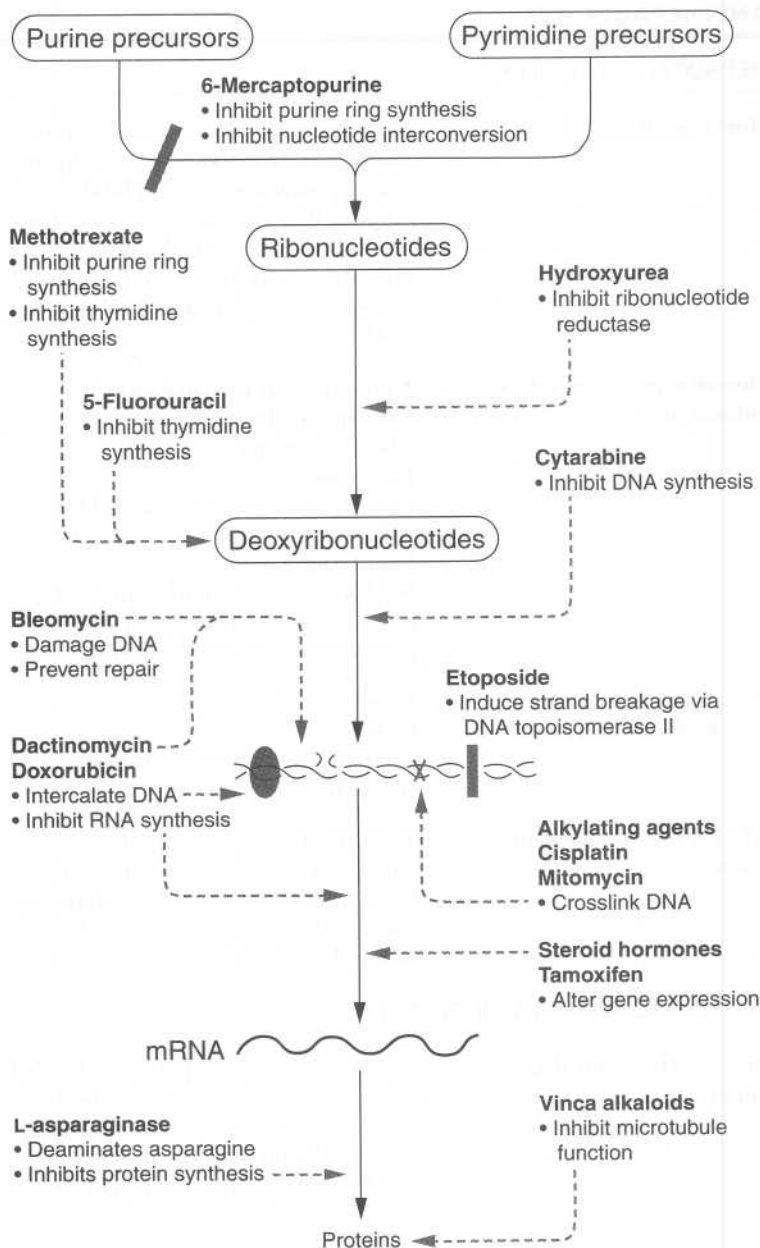


Figure 39-2. Cancer chemotherapeutics and their sites of action. (Adapted and redrawn from Stanbury J et al: *Metabolic Basis of Inherited Disease*, 4th ed. New York, McGraw-Hill, 1989, Fig 27—45. Used with permission of The McGraw-Hill Companies.)

Describe the adverse effects. Bone marrow suppression and hepato-toxicity

CYTARABINE (CYTOSAR-U)

How does this drug function? Cytarabine is a pyrimidine analog that enters cells and is then activated by phosphorylation. The triphosphate form (ARA-CTP) then prevents DNA synthesis by blocking chain elongation.

What is its clinical use? Cytarabine is very much limited to treating AML.

What is the route of administration? Intravenous

Describe the adverse effects. Severe bone marrow suppression
Stomatitis
Gastrointestinal distress

5-FLUOROURACIL (ADRUCIL)

How does this drug work? Like cytarabine, 5-fluorouracil acts as a pyrimidine analog. It enters cells and is converted to 5FdUMP, which then inhibits the enzyme **thymidylate synthetase**. The result is inhibition of DNA synthesis through lack of thymine nucleotides. 5FdUMP also inhibits RNA synthesis.

State the clinical use. Treatment of breast carcinoma and GI (gastric, pancreatic, and colorectal) carcinomas

Describe the adverse effects. Myelosuppression, stomatitis, and oral and GI mucosa ulcers

HYDROXYUREA (HYDREA)

What is it? Hydroxyurea is a urea analogue that prevents DNA synthesis by inhibiting the enzyme ribonucleotide reductase.

How is this drug used clinically? For treating CML, polycythemia vera, and melanoma

What are the adverse effects?

Bone marrow suppression
Nausea and vomiting
Diarrhea

HORMONES AND RELATED AGENTS

FLUTAMIDE (EULEXIN)

How does flutamide work?

It is a nonsteroidal antiandrogen that inhibits translocation of the androgen receptor to the nucleus.

What are the clinical uses?

Flutamide is used in combination with GnRH such as leuprolide for the treatment of prostate cancer.

State the adverse effects.

Diarrhea
Hot flashes
Impotence
Gynecomastia
Reversible hepatotoxicity

TAMOXIFEN (NOLVADEX)

What is it?

A nonsteroidal antiestrogen that competitively inhibits estradiol at estrogen receptors

How is tamoxifen used clinically?

It is the drug of choice for women with estrogen receptor-positive breast cancer.

State the route of administration.

Oral

What are the adverse effects?

Hot flashes, GI effects (nausea and vomiting), and menstrual bleeding. Long-term effects include thromboembolic disease and possibly endometrial cancer.

LEUPROLIDE (LUPRON)

How does this drug work?

Leuprolide is a long-acting synthetic gonadotropin-releasing hormone analogue that, when administered in a continuous fashion, is used to inhibit the release of FSH and LH from the anterior pituitary.

What is its clinical use?	Treating prostate cancer and endometriosis
Are there adverse effects?	Yes—hot flashes and impotence

GLUCOCORTICOIDS

Give two examples of glucocorticoids used as antineoplastic agents.	<ol style="list-style-type: none"> 1. Prednisone 2. Hydrocortisone
What are their clinical uses?	Treatment of Hodgkin's lymphoma, non-Hodgkin's lymphoma, ALL, and myeloma
List the adverse effects.	Increased incidence of infection Hyperglycemia Osteoporosis Gastric and duodenal ulcers See <i>Chapter 32—Corticosteroids and Inhibitors</i> for more information on glucocorticoids.

PLANT ALKALOIDS

VINBLASTINE (VELBAN) AND VINCRISTINE (ONCOVIN)

Describe the mechanism of action.	Both of these drugs also known as vinca alkaloids, bind tubulin, and prevent the assembly of microtubules. This inhibits formation of the mitotic spindle and arrests the cell at metaphase.
What is the clinical use?	<p>Vinblastine—component of a protocol for Hodgkin's disease and VBC [vinblastine, bleomycin, cisplatin] regimen for testicular carcinoma</p> <p>Vincristine—component of MOPP for Hodgkin's lymphoma and regimens used to treat childhood lymphatic leukemias, Wilms' tumor, and Ewing's sarcoma</p>
How are these two drugs administered?	Intravenously
Does resistance occur?	Yes. Resistant tumor cells are often found to have increased levels of P-glycoprotein, a membrane transport pump that causes the efflux of vinblastine and vincristine.

Are there adverse effects?

Vinblastine produces more bone marrow suppression than does vincristine.

Vin**B**lantine—**B**one marrow suppression

Vincristine induces a peripheral neuropathy.

Both drugs can cause phlebitis or cellulitis



ETOPOSIDE (VEPESID)

What is etoposide's mechanism of action?

It inhibits the function of the DNA topoisomerase II-DNA complex, which causes single-stranded DNA breaks during DNA replication.

How is etoposide used clinically?

It is used for small cell carcinoma of the lung, testicular carcinoma, Kaposi's sarcoma, and non-Hodgkin's lymphoma.

State the adverse effects.

Nausea and vomiting

Alopecia

Bone marrow suppression (leukopenia, thrombocytopenia)

PACLITAXEL (TAXOL)

How does paclitaxel work?

This drug binds tubulin and **promotes** the formation of microtubules and preventing their disassembly. The result is that bundles of malformed microtubules are created, which arrests the cell in mitosis.

What is the clinical use?

Paclitaxel is used for treating ovarian and breast carcinoma.

List the adverse effects.

Bone marrow suppression

GI effects (nausea and vomiting)

Arthralgias

Peripheral neuropathy

Section X

Antimicrobial Drugs

Introduction to Antimicrobial Drugs

What are four critical factors that determine the selection of an antimicrobial drug?

1. **Identity of the organism**—usually identified through Gram stain or culture
2. **Safety of the drug**
3. **Site of infection**—for example, some drugs cross the blood-brain barrier whereas others do not.
4. **Patient's medical history**—allergies, immune status, renal and hepatic condition, pregnancy, and lactation status

See *Appendix B—Recommended Antimicrobial Agents Against Selected Organisms* at the back of this book and *Appendix C—comparison of antimicrobial spectra*.

Name four large classes of antimicrobial agents, give examples of each, and describe their mechanisms of action.

1. **Cell wall synthesis inhibitors**—
Examples: Penicillins, cycloserine, cephalosporins, vancomycin. These drugs block the cross-linking of peptidoglycan chains, which is the final step in bacterial cell wall synthesis.
2. **Protein synthesis inhibitors**—
Examples: Tetracycline, aminoglycosides, erythromycin, clindamycin, chloramphenicol. These agents bind to bacterial ribosomes.
3. **DNA synthesis inhibitors**—
Quinolones and fluoroquinolones block nucleic acid synthesis by inhibiting DNA gyrase. Rifampin inhibits DNA-dependent RNA polymerase. The sulfonamides inhibit synthesis of folate, which is a critical component of DNA.

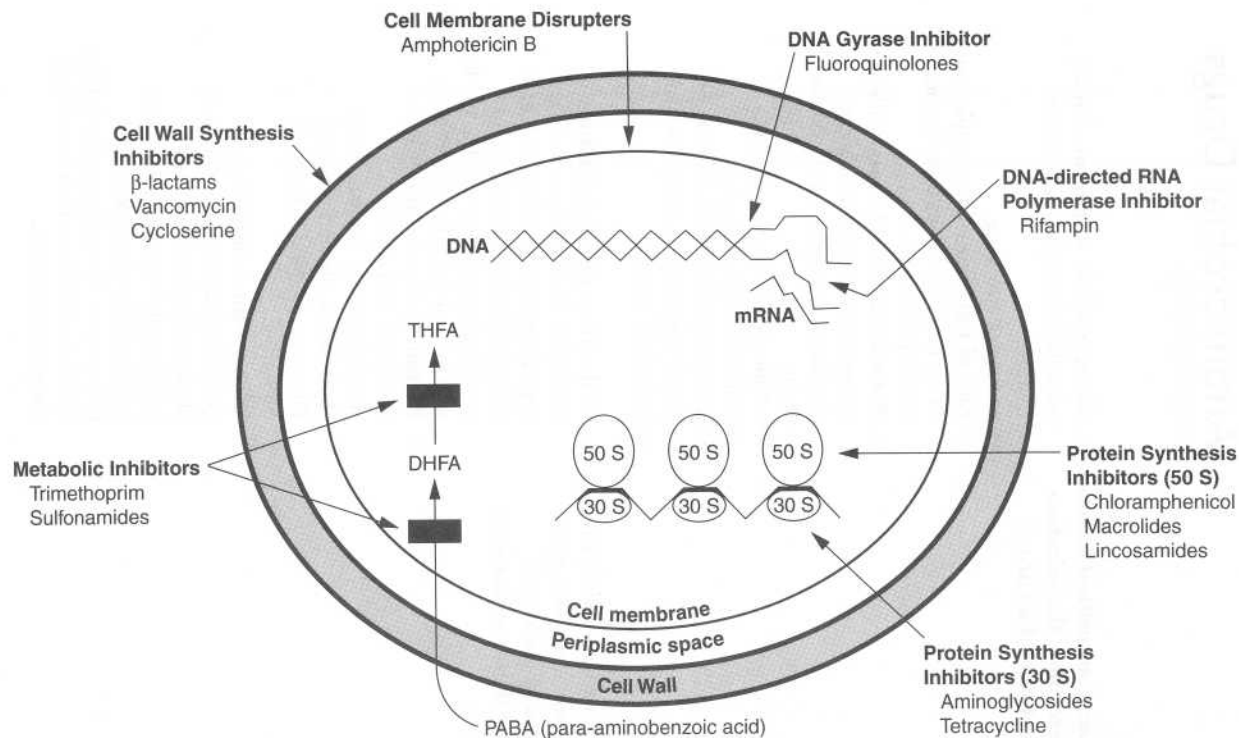


Figure 40-1. Site of action of various antimicrobial agents. (Redrawn from Gallia G, Hann CL, Hewson WH: *The Pharmacology Companion*. Alert & Oriented Publishing Company, 1997, p 150, Fig 5.1.)

4. **Cell membrane disrupter**—Polyene antimicrobials such as amphotericin B bind to components of fungal cell membranes.

See Figure 40–1.

Each of these groups is discussed in detail in succeeding chapters.

What do bacteriostatic drugs do?

They arrest the growth and replication of bacteria, thus giving the body's immune system a chance to destroy and remove the pathogens.

What do bactericidal drugs do?

Bactericidal drugs kill bacteria outright.

Which drugs are considered bactericidal?

Aminoglycosides
Quinolones
Cycloserine
Vancomycin
Carbapenems
Penicillins
Cephalosporins

Which drugs are considered bacteriostatic?

Chloramphenicol
Nitrofurantoin
Clindamycin
Tetracycline
Erythromycin
Trimethoprim
Lincomycin

What is meant by the chemotherapeutic spectrum of an antibiotic?

The term *chemotherapeutic spectrum* refers to the types of microorganisms that are affected by that agent. Thus, a broad-spectrum agent affects a wide variety of microorganisms. See *Appendix C—Comparison of Antimicrobial Spectra* at the end of this book.

Can antibiotics be used in combination?

Yes! Sometimes, for example, in the empiric treatment of pneumonia, combination drug therapy is required. However, whenever possible it is best to use single-agent therapy to limit the risk of toxicity and resistance.

What is drug resistance?

The term *drug resistance* refers to the ability of a microorganism to withstand a drug that was previously toxic to it.

Name the four basic mechanisms by which microorganisms can become resistant to antibiotics, and give an example of each.

1. **Production of drug-inactivating enzymes**— β -lactamase, an enzyme that binds to certain penicillins, is a prime illustration of an enzyme that counteracts the effects of an antibiotic.
2. **Changes in drug penetration**—The effectiveness of aminoglycosides and tetracycline, for example, depends on their ability to reach high intracellular concentrations. Bacteria may adapt to become impermeable to these antibiotics or increase their ability to excrete these antibiotics.
3. **Changes in receptor structure**—Antibiotics such as erythromycin bind to certain receptors. Microorganisms can sometimes cause these receptors to mutate so that they have very little affinity for antibiotics.
4. **Alterations of metabolic pathways**—Bacteria may acquire the ability to use preformed folic acid, bypassing the inhibitory actions of sulfonamides.

What is meant by empiric therapy?

Early intervention through the use of an antibiotic before a pathogen is identified

What is the benefit of empiric therapy?

Because early intervention usually helps to improve the outcome of an infection, antibiotics are sometimes used before a Gram's stain or culture of the pathogen is obtained. Physicians use information from the history, physical examination, and any other completed diagnostic tests to determine which antibiotic to use.

What is meant by antimicrobial prophylaxis?

Antimicrobial prophylaxis is the use of antibiotics to *prevent* disease. Examples include prevention of tuberculosis among individuals who are in close contact with infected patients, and pretreatment of patients with artificial heart valves who are undergoing dental procedures.

41

Penicillins

To what classification of drug does penicillin belong?

Penicillin is a member of a group of drugs known as β -lactams because of their characteristic four-membered lactam ring (Figure 41-1).

Define β -lactamase.

β -lactamase is a bacterial enzyme that hydrolyzes the amide bond of the β -lactam ring. It is also known as penicillinase.

What are penicillin-binding proteins (PBPs)?

Penicillin-binding proteins are enzymes that are involved in the synthesis of the cell wall and in the maintenance of the morphologic structure of bacteria.

What are transpeptidases?

Transpeptidases are bacterial enzymes responsible for cross-linking peptidoglycan chains, which is the final step in bacterial cell wall synthesis.

What is the major mechanism by which penicillins kill bacteria?

Penicillins bind to PBPs and inhibit the transpeptidase step, which results in bacterial cell lysis.

What additional mechanism is involved?

Penicillins also release autolysins, which are bacterial degradative enzymes that are involved in the normal remodeling of the bacterial cell wall.

Which type of organisms are *not* susceptible to penicillins?

Organisms that are not actively growing or do not have a cell wall

Do penicillins enter the central nervous system?

Normally these drugs do not distribute well into the CNS. However, when the meninges are inflamed, as occurs in meningitis, penicillins easily reach therapeutic concentrations within the CNS.

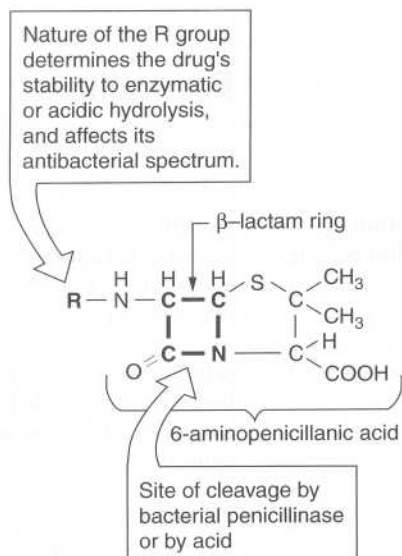


Figure 41–1. Structural features of β-lactam antibiotics. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 297.)

How are the penicillins classified?

Penicillins, some of the most common and important antibiotics, can be classified as follows:

Natural penicillins
 Antistaphylococcal penicillins
 Antipseudomonal penicillins
 Extended-spectrum penicillins

NATURAL PENICILLINS

Give four examples of natural penicillins and their routes of administration.

1. Penicillin G, the prototype drug—oral, intravenous, intramuscular
2. Penicillin V—oral only
3. Penicillin G procaine (Crysticillin A.S.)—intramuscular only
4. Penicillin G benzathine (Bicillin L-A)—intramuscular only

How do the various natural penicillins differ from each other?

These drugs all work the same way; they differ in their route of administration and stability to gastric acid.

What can natural penicillin be used for?

Natural penicillin has a large spectrum; however, it affects gram-positive organisms the most. Clinical indications include the following infections:

- Streptococci
- Meningococci
- Clostridium
- Listeria
- Enterococci
- Diphtheria
- Anthrax
- Syphilis
- Spirochetes such as *Treponema pallidum*
- Actinomycosis
- Bacteroides* species (except *Bacteroides fragilis*)
- Anaerobic organisms that do not produce β -lactamase

Describe the absorption of these penicillins.

Absorption depends on their acid stability and protein binding.

Is the absorption of penicillins influenced by food?

Absorption of most penicillins is affected by food; therefore, these drugs (except amoxicillin) should be administered at least 1 to 2 hours before or after a meal.

How are these drugs excreted?

Penicillins are mostly unchanged as they are excreted in the urine (by glomerular filtration and active tubular secretion), although some penicillins, such as nafcillin and ampicillin, undergo hepatic inactivation and are excreted in the bile.

How can excretion of penicillins be altered?

Excretion by renal tubular secretion can be delayed by co-administration of probenecid, which inhibits the organic acid secretion system.

What are the most common adverse effects seen with patients who are medicated with penicillin?

Hypersensitivity reactions—anaphylaxis (rare), urticaria, severe pruritus, fever, joint swelling, and bronchospasm—are the number-1 toxicity to watch for.

Seizures may occur in patients with poor renal function, or in newborns who have immature anion transport systems

Gastrointestinal disturbances—diarrhea

Hemolytic anemia

Cation toxicity—Because penicillins are combined with sodium or potassium, patients may suffer from excess Na^+ or K^+ (only seen with extremely high doses).

Are these adverse effects seen with all forms of penicillins?

Yes! Remember that these toxicities apply to all forms of penicillins, not just natural penicillins. (Additional or unique toxicities are mentioned later.)

ANTISTAPHYLOCOCCAL PENICILLINS (PENICILLINASE-RESISTANT PENICILLINS)

Give some examples of penicillinase-resistant drugs and indicate their routes of administration.

Methicillin (Staphcillin)—IV or IM *only*
 Nafcillin (Unipen)—PO, IV, or IM
 Oxacillin (Bactocill)—PO, IV, or IM
 Dicloxacillin (Dynapen)—PO, IV, or IM
 Cloxacillin (Tegopen)—PO, IV, or IM
 Remember—these are the *only* penicillins that by themselves are resistant to penicillinase.

When do you use penicillinase-resistant penicillins?

These drugs have a very narrow spectrum; they were developed solely for the purpose of killing staphylococci that produce penicillinase.

What should you do if you encounter methicillin-resistant *Staphylococcus aureus*?

Use vancomycin immediately for serious infections.

What is the distinctive toxicity of methicillin?

Interstitial nephritis

What other toxicity is associated with these drugs?

Methicillin, nafcillin, and some other penicillins occasionally cause granulocytopenia, especially in children.

ANTIPSEUDOMONAL PENICILLINS

Give five examples of antipseudomonal penicillins.

1. Mezlocillin (Mezlin)
2. Piperacillin (Pipracil)
3. Azlocillin (Azlin)
4. Carbenicillin (Geopen)
5. Ticarcillin (Ticar)

What is the route of administration for mezlocillin, piperacillin, azlocillin, and ticarcillin?	All of these drugs are extremely unstable in gastric acid and therefore must be given intravenously or intramuscularly.
What is the route of administration for carbenicillin?	IV and IM (Geopen) as well as PO (Geocillin)
Are these drugs inactivated by penicillinase?	Yes
What is their antimicrobial spectrum?	Gram-negative bacilli, especially <i>Pseudomonas</i> species (hence the name). <i>Klebsiella</i> is an exception because it produces penicillinase.
What toxicity is likely to be seen with ticarcillin and carbenicillin?	Platelet dysfunction

EXTENDED-SPECTRUM PENICILLINS

Give some examples of extended-spectrum penicillins, and indicate their routes of administration.	Amoxicillin (Amoxil)—PO Ampicillin (Omnipen)—PO, IV, and IM
What organisms can ampicillin and amoxicillin be used against?	In general, all of the organisms affected by the natural penicillins plus some β -negative organisms such as <i>E. coli</i> , <i>Proteus mirabilis</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>H. influenzae</i> , and <i>Listeria monocytogenes</i> .
Are these drugs inactivated by β -lactamase?	Yes!
What important toxicities are associated with ampicillin?	In patients with mononucleosis, the incidence of rash is extremely high. Ampicillin-induced pseudomembranous colitis is another potential side-effect.
With what other agents are these two drugs often combined?	β -lactamase inhibitors, which inhibit the enzyme by binding to it and thus protecting the accompanying antibiotic. On their own, β -lactamase inhibitors are not effective in eliminating bacteria.

Give three examples of β -lactamase inhibitors.

1. Clavulanic acid
2. Sulbactam
3. Tazobactam

What drugs are each of the three β -lactamase inhibitors paired with?

Clavulanic acid with amoxicillin (Augmentin) or with ticarcillin (Timentin)
 Sulbactam with ampicillin (Unasyn)
 Tazobactam with piperacillin (Zosyn)

RESISTANCE

Aside from inactivation of the antibiotic by β -lactamase, how else does bacterial resistance develop?

Alteration in target PBPs
 Decreased cell permeability, which prevents the penetration of the antibiotic to its target

42

Cephalosporins and Other Cell Wall Synthesis Inhibitors

Where did cephalosporins originate?

From the *Cephalosporium* fungi

How do they work?

They are analogous to penicillins in:

- Binding to specific penicillin-binding proteins
- Inhibition of cell wall synthesis by blocking the transpeptidase step of peptidoglycan synthesis
- Activation of autolytic enzymes

Are cephalosporins bactericidal or bacteriostatic?

Bactericidal

How are cephalosporins subdivided?

Into first, second, and third generations. These classifications are based on general features of antimicrobial activity (Figure 42-1).

In general, how do the characteristics of cephalosporins change from first to third generation agents?

From the first generation to the third generation of cephalosporins, there is:

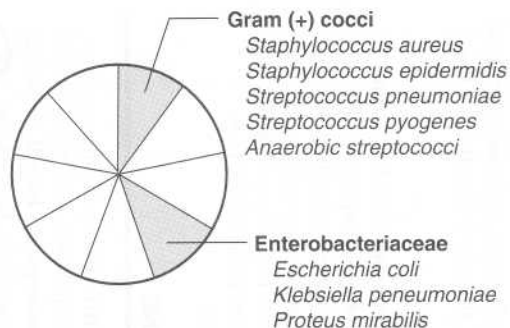
- A decrease in gram-positive coverage
- An increase in gram-negative coverage
- An increase in CNS penetration
- An increase in resistance to β -lactamase

FIRST-GENERATION CEPHALOSPORINS

First-generation cephalosporins are active against which organisms?

Gram-positive cocci, including pneumococci, streptococci, and staphylococci
Some **gram-negative bacilli**, including *Proteus mirabilis*, *Escherichia coli*, and *Klebsiella*—PEcK





First Generation

Cefazolin

Cefadroxil

Cephalexin

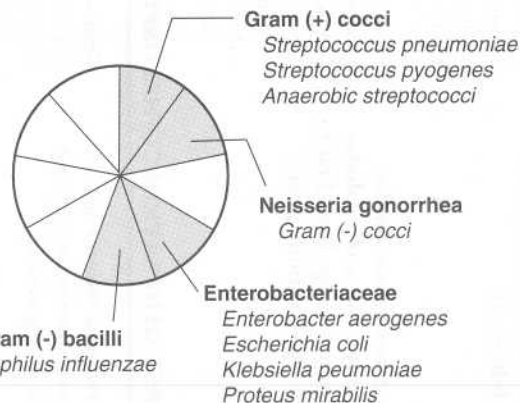
Cephalothin

Cephapirin

Cephradine

This first-generation parenteral cephalosporin has a longer duration of action and a similar spectrum of action compared to other first-generation drugs. Good penetration into bone.

Prototype of first-generation oral cephalosporins. Oral administration twice daily is effective against pharyngitis.



Second Generation

Cefaclor

Cefamandole

Cefonicid

Cefmetazole

Cefotetan

Cefoxitin

Cefuroxime

Cefuroxime axetil

Shows good activity against anaerobes, particularly *Bacteroides fragilis*. Useful in patients with intra-abdominal sepsis, and against gynecologic sepsis including pelvic inflammatory disease.

This prototype second-generation parenteral cephalosporin has a longer half-life than similar agents. It crosses the blood-brain barrier and can be used for community-acquired bronchitis or pneumonia in the elderly and for patients who are immunocompromised.

Oral administration twice daily. Well absorbed. Active against β -lactamase-producing organisms.

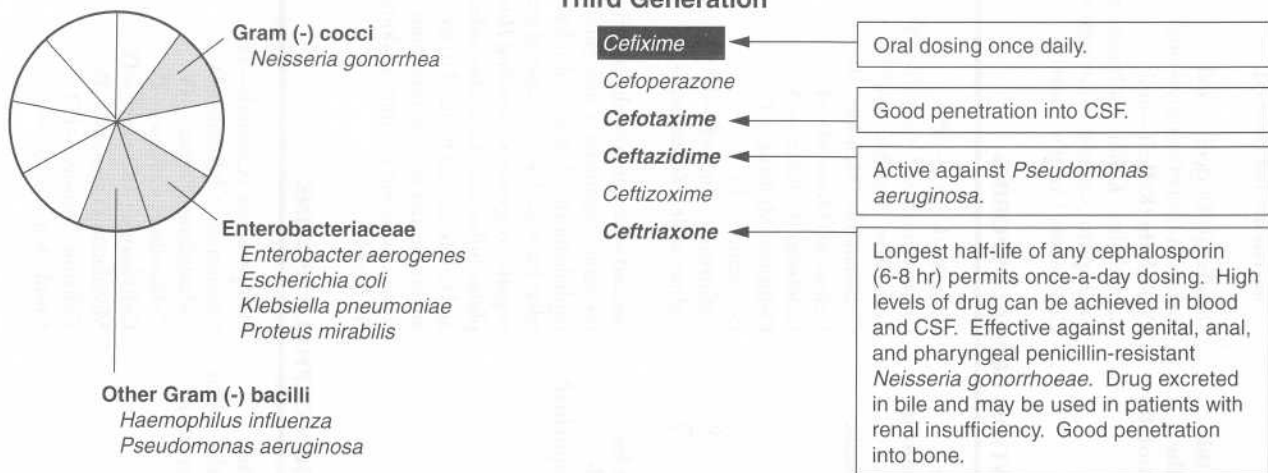


Figure 42-1. Characteristics of some clinically useful cephalosporins. Drugs that can be administered orally are shown in reverse type. Drugs with unique traits are shown in bold. (Adapted and redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 305.)

Bacteroides fragilis, enterococci, and methicillin-resistant *Staphylococcus aureus* are not covered.

Which drugs are in this group, and what is the route of administration for each?

Cefadroxil (Duricef)—oral
Cefazolin (Ancef)—intravenous
Cephalexin (Keflex)—oral
Cephalothin (Keflin)—intravenous
Cephapirin (Cefadyl)—intravenous
Cephradine (Anspor)—oral

SECOND-GENERATION CEPHALOSPORINS

Name some second-generation cephalosporins and state the route of administration for each.

Cefaclor (Ceclor)—PO
Cefuroxime axetil (Ceftin)—PO
Loracarbef (Lorabid)—PO
Cefamandole (Mandol)—IV
Cefonicid (Monocid)—IV
Cefotetan (Cefotan)—IV
Cefoxitin (Mefoxin)—IV
Ceforanide—IV
Cefuroxime (Zinacef)—IV
Cefmetazole (Zefazone)—IV

What infections can be treated with second-generation cephalosporins?

Second-generation cephalosporins cover the same organisms as first-generation cephalosporins, but they also have somewhat increased activity against gram-negative organisms including *Haemophilus influenzae*. Cefoxitin, cefmetazole, and cefotetan can be used to treat anaerobic and aerobic infections, such as those that affect the intra-abdominal area (*B. fragilis*)

THIRD-GENERATION CEPHALOSPORINS

What drugs are in this group, and what is the route of administration for each?

Cefoperazone (Cefobid)—IV
Cefotaxime (Claforan)—IV
Ceftazidime (Fortaz)—IV
Ceftizoxime (Cefizox)—IV
Ceftriaxone (Rocephin)—IV
Moxalactam (Moxam)—IV
Cefixime (Suprax)—PO
Ceftibuten (Cedax)—PO

Against what organisms do these agents exert action?

Third-generation cephalosporins provide expanded gram-negative coverage but

poor gram-positive coverage. They are good against *Enterobacter*, *Citrobacter*, and *Providencia*, as well as β -lactamase-producing strains of *Neisseria* and *Haemophilus*. *Pseudomonas* infection can be treated with ceftazidime and cefoperazone.

GENERAL FEATURES OF THE CEPHALOSPORINS

What are these agents inactive against?

All cephalosporins are inactive against enterococci, methicillin-resistant staphylococci, *Listeria monocytogenes*, and *Clostridium difficile*.

How are the cephalosporins primarily excreted?

Through glomerular filtration. Cefoperazone and ceftriaxone are exceptions; they are excreted in bile.

In general, what are the adverse effects of the cephalosporins?

Hypersensitivity reactions similar to those induced by penicillins (bronchospasm, urticaria)

Nephrotoxicity—more common with high doses of cephalothin

Intolerance to alcohol (a disulfiram-type reaction) with cefamandole, cefotetan, moxalactam, and cefoperazone

A positive Coombs' test result, but rarely associated with hemolytic anemia

Hypothrombinemia with cefamandole, cefoperazone, and moxalactam due to vitamin K inhibition

OTHER CELL WALL SYNTHESIS INHIBITORS

MONOBACTAMS AZTREONAM (Azactam)

Describe the mechanism of action of the monobactams.

Monobactams disrupt bacterial cell wall synthesis by binding to penicillin-binding proteins and inhibiting peptidoglycan synthesis.

Describe the pharmacokinetics of aztreonam.

Aztreonam is administered via IV or IM routes, and is excreted in the urine.

What are the clinical indications for aztreonam?

Primarily aerobic gram-negative rods

What are the adverse effects of aztreonam?	Skin rash Elevated liver function enzymes Gastrointestinal distress (nausea, vomiting)
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CARBAPENEMS

What are they?	Carbapenems are synthetic β -lactam antibiotics that are structurally related to the penicillins. They are, however, resistant to β -lactamase.
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Give an example of a carbapenem.	Imipenem (Primaxin)
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What is the antibacterial spectrum of this drug?	Imipenem is active against virtually all gram-positive, gram-negative, and anaerobic organisms; methicillin-resistant staphylococcus and <i>Clostridium difficile</i> are important exceptions.
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What is imipenem usually combined with, and why?	Imipenem is usually combined with cilastatin . Imipenem is inactivated by the enzyme dehydropeptidase, which is found in the brush border of the proximal tubule. Cilastatin prevents this inactivation and allows imipenem to be used for the treatment of urinary tract infections.
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Describe imipenem's adverse effects.	Seizures—provoked by high levels of imipenem GI effects—nausea, vomiting, diarrhea Eosinophilia and neutropenia
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VANCOMYCIN

What is vancomycin's mechanism of action?	Vancomycin binds to the D-alanyl-D-alanine portion of cell wall precursors and inhibits peptidoglycan polymerization.
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Describe this agent's antibacterial spectrum.	Vancomycin is effective against all gram-positive organisms. Presently it is reserved for treating severe infections caused by methicillin-resistant staphylococci or serious gram-positive infection in penicillin-allergic patients. It is also used to treat <i>C. difficile</i> -induced pseudo-
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	membranous colitis and for prophylaxis in patients with prosthetic heart valves who are undergoing oral surgery.
How does resistance to vancomycin develop?	Primarily through plasmid-mediated changes in permeability to the drug, and decreased binding of vancomycin to receptor molecules
What is vancomycin's usual route of administration?	IV, except when treating pseudomembranous colitis, when it is given orally
How is it excreted?	Ninety percent is excreted through glomerular filtration.
What are the adverse effects?	<p>Fever and chills</p> <p>Shock—a result of rapid administration</p> <p>Dose-related ototoxicity and nephrotoxicity—rare with today's preparations</p> <p>Red man's syndrome—facial flushing and hypotension due to a rapid infusion of the agent, thought to be caused by histamine release</p>

BACITRACIN

Describe this agent's anti-microbial spectrum.	Bacitracin is used against gram-positive organisms.
How does bacitracin work?	It inhibits cell wall synthesis by blocking the transfer of peptidoglycan subunits to a growing cell wall.
What is the usual route of administration?	Bacitracin's use is restricted to topical application because of its potential for nephrotoxicity if it is given systemically.
Are there adverse reactions?	Yes—nausea/vomiting, and skin rash

CYCLOSERINE

How does cycloserine work?	Cycloserine is a structural analog of D-alanine and therefore blocks the incorporation of D-alanine into peptidoglycans.
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When is this drug used?

Cycloserine is effective against many gram-positive and gram-negative organisms, but it is almost always used to treat tuberculosis caused by strains of *Mycobacterium tuberculosis* that are resistant to first-line drugs.

What are its toxicities?

CNS toxicity—tremors, seizures, confusion, headaches, psychosis

43

Protein Synthesis Inhibitors

How do protein synthesis inhibitors work?

By targeting bacterial ribosomes

Why don't protein synthesis inhibitors work on eukaryotic cells?

Eukaryotic cells have 80S ribosomes composed of 60S and 40S subunits, whereas bacterial cells have 70S ribosomes composed of 50S and 30S subunits. This structural difference allows for selective toxicity. (°S stands for Svedburg unit of sedimentation coefficient.)

Can high doses of drugs such as chloramphenicol and tetracycline result in adverse effects on eukaryotic cells?

Yes, because the eukaryotic mitochondrial ribosome somewhat resembles the bacterial ribosome.

Which antibiotics work on the bacterial 30S ribosomal subunit?

Aminoglycosides
Tetracyclines
Spectinomycin

Which antibiotics work on the bacterial 50S ribosomal subunit?

Chloramphenicol
Macrolides—erythromycin (E-Mycin),
clarithromycin (Biaxin), azithromycin
(Zithromax)
Lincosamides—clindamycin

AMINOGLYCOSIDES

Give some examples of aminoglycosides.

Amikacin (Amikin)
Netilmicin (Netromycin)
Neomycin (Mycifradin)
Tobramycin (Nebcin)
Gentamicin (Garamycin)
Streptomycin

What is the mechanism of action?

Aminoglycosides cross the outer membrane and enter the periplasmic space through aqueous channels formed by porin proteins. These drugs are then actively transported through the cell membrane by an oxygen-dependent process. They then irreversibly bind to the 30S ribosomal subunit and inhibit protein synthesis by blocking the formation of the initiation complex and the translocation step (Figure 43-1).

What are the pharmacokinetics of the aminoglycosides?

The aminoglycosides penetrate most body fluids well, except for the CSF. High concentrations of these drugs tend to accumulate in the renal cortex and endolymph of the inner ear, which could account for their nephrotoxicity and ototoxicity.

How are these drugs administered?

Aminoglycosides are usually given IV, because they are poorly absorbed after oral administration. Neomycin is an exception: it is given topically.

Describe the metabolism of the aminoglycosides.

These drugs are excreted unchanged by the kidneys.

What is the therapeutic use?

Aminoglycosides are used primarily against aerobic gram-negative enteric bacteria such as *Escherichia coli*, *Enterobacter*, and *Klebsiella*. They can also be used against *Pseudomonas aeruginosa*. The aminoglycosides do not cover anaerobes because oxidative metabolism is required for uptake of these drugs. Frequently, aminoglycosides are co-administered with β -lactams to extend the spectrum and take advantage of the synergism between these two classes of drugs.

Are there any toxicities with the aminoglycosides?

Ototoxicity—This is directly related to plasma levels and duration of treatment.

Nephrotoxicity—Severe acute tubular necrosis may occur.

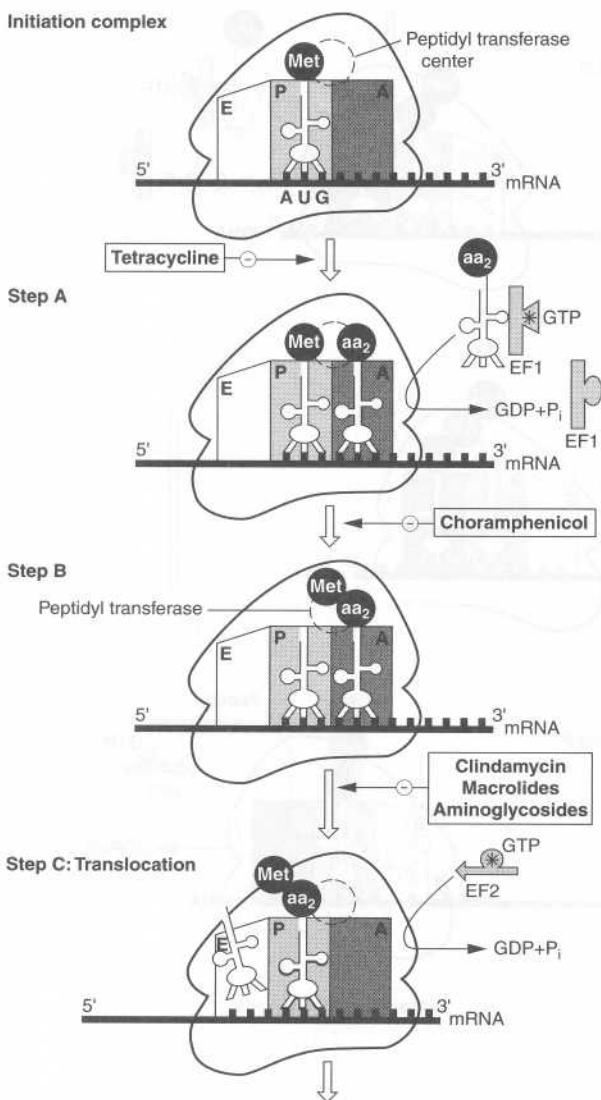


Figure 43-1. Elongation steps in protein synthesis. The first and second cycles of elongation are shown. In *Step A*, aminoacyl-tRNA is placed in the ribosomal A site, beside the P site methionyl-tRNA of the completed initiation complex. In *Step B* the first peptide bond is formed, and in *Step C* the mRNA-peptidyl tRNA complex is translocated to the P site while the deacylated initiator tRNA is moved to the E site. Binding of the next aminoacyl-tRNA (*Step D*) may cause release of deacylated tRNA from the E site, or it may remain in place during peptide bond formation (*Step E*) and then be displaced during translocation (*Step F*). Additional amino acids are added by successive repetition of Steps D-F. EF = elongation factors. (Redrawn from Devlin T: *Textbook of Biochemistry with Clinical Correlations*. New York, Wiley-Liss, 1992, p 740. Adapted with permission of Wiley-Liss, Inc., a division of John Wiley & Sons, Inc.)

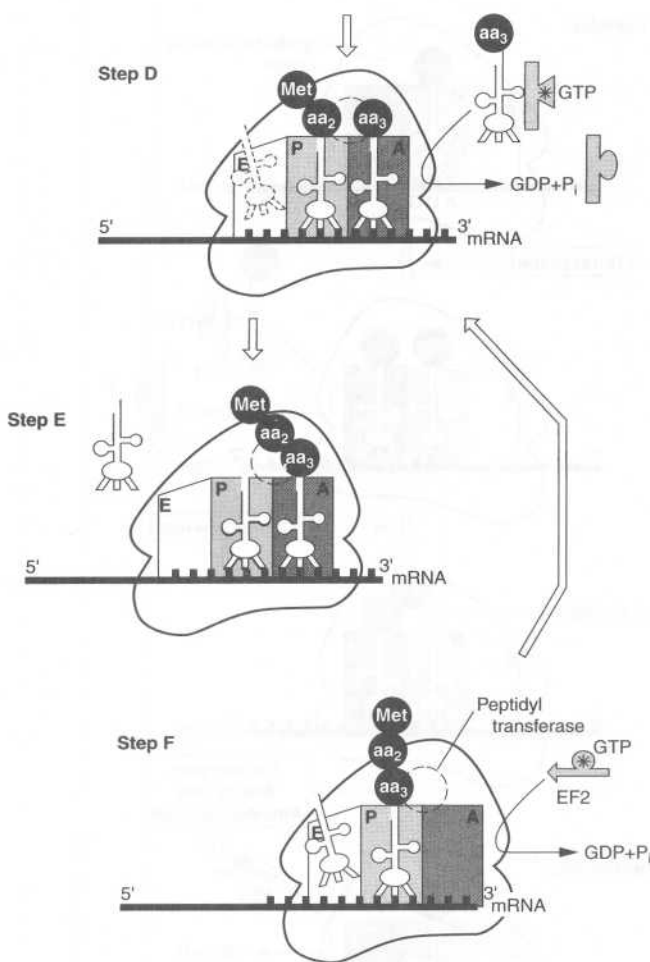


Figure 43-1 (continued)

Neuromuscular blockade—Aminoglycosides may cause respiratory paralysis after larger-than-recommended doses.

Because of the severe side effects of aminoglycosides, it is absolutely critical to monitor peak and trough plasma levels.

TETRACYCLINES

Give some examples of tetracyclines.

Tetracycline (Sumycin)
Doxycycline (Vibramycin)
Demeclocycline (Declomycin)
Minocycline (Minocin)
Oxytetracycline (Terramycin)

Describe the mechanism of action of the tetracyclines.

Tetracyclines bind reversibly to the 30S subunit of bacterial ribosomes, blocking aminoacyl transfer RNA from entering the acceptor site on the mRNA-ribosomal complex (see Figure 43-1).

What is the antibiotic spectrum of the tetracyclines?

Tetracyclines are broad-spectrum antibiotics that are bacteriostatic for many gram-positive and gram-negative bacteria, including anaerobes, chlamydiae, mycoplasmas, and rickettsiae.

How are the tetracyclines administered?

They are adequately absorbed after oral administration, *except* after the consumption of dairy foods, iron-containing preparations, or antacids that contain Ca^{2+} , Al^{3+} , Mg^{2+} , or Fe^{2+} .

Describe the metabolism of the tetracyclines.

Tetracyclines are mainly excreted in urine, but doxycycline is a notable exception; it is excreted via the gastrointestinal tract.

How does resistance to tetracyclines develop?

Bacteria can develop resistance through three primary mechanisms:

1. Inability of the drug to accumulate intracellularly, either through an increased efflux by an active transport protein pump or diminished influx. *This mechanism is the most important of the three to remember.*
2. Inability of the drug to bind to the bacterial ribosome
3. Enzymatic destruction of the drug

List the adverse effects of tetracycline administration.

GI effects—Nausea and vomiting are the most common symptoms.

Bony structures and teeth—

Tetracyclines are readily deposited in bone and teeth during calcification,

which can lead to discoloration and hypoplasia of teeth in growing children.

Liver toxicity—Patients who are pregnant or who have preexisting liver insufficiency may experience hepatic necrosis when given high doses of tetracyclines.

Photosensitivity—Demeclocycline can induce hypersensitivity to sunlight or ultraviolet light.

Vestibular reactions—Dizziness, nausea, and vomiting can occur with minocycline or doxycycline administration.

Name a major contraindication to the use of tetracyclines.

Pregnancy

SPECTINOMYCIN (Trobicin)

What is spectinomycin?

An aminocyclitol antibiotic that is structurally related to aminoglycosides

Describe the mechanism of action.

It binds to the 30S ribosomal subunit and inhibits protein synthesis.

What is spectinomycin's route of administration?

IM injection

State the clinical use of spectinomycin.

This drug is used as an alternative treatment for *Neisseria gonorrhoeae* in patients who are allergic to ceftriaxone or who have a resistant strain of gonorrhea. The **spectrum of spectinomycin** is narrow—it only covers *Neisseria*.



What are the adverse effects?

Pain at the injection site
Occasional fever with nausea

CHLORAMPHENICOL (Chloromycetin)

Describe chloramphenicol.

It is a bacteriostatic broad-spectrum antibiotic.

What is its mechanism of action?

It binds reversibly to the 50S ribosomal subunit and inhibits protein synthesis during the peptidyl transferase reaction (see Figure 43–1).

What is chloramphenicol effective against?

It is active against both aerobic and anaerobic gram-positive and gram-negative organisms, as well as *Rickettsia*, *Haemophilus influenzae*, *Neisseria meningitidis*, and *Bacteroides* species are particularly susceptible to chloramphenicol. Despite this wide range of coverage, chloramphenicol is used very rarely because of its serious side-effects.

How does resistance to this drug develop?

Clinically significant resistance is due to bacterial production of chloramphenicol acetyltransferase, an enzyme that inactivates chloramphenicol or decreases penetration of the drug.

Describe the metabolism of this drug.

Chloramphenicol is metabolized in the liver.

Are there adverse reactions?

Yes. The clinical use of chloramphenicol has declined because of the serious adverse effects associated with its administration, which include:
Gray baby syndrome, which is characterized by cyanosis, vomiting, green stools, and vasomotor collapse caused by accumulation of unmetabolized drug. (The neonatal liver has not yet synthesized sufficient glucuronidase to detoxify many drugs.)
Bone marrow suppression
Aplastic anemia (rare, but can be fatal)
Hemolytic anemia

MACROLIDES

Which drugs are included in this category?

Erythromycin (E-Mycin)—the prototype macrolide
Clarithromycin (Biaxin)
Azithromycin (Zithromax)
Both azithromycin and clarithromycin are newer derivatives of erythromycin.

How do macrolides work?	By binding to the 50S ribosome and inhibiting the translocation step of protein synthesis (see Figure 43–1). This action is bacteriostatic for some organisms, bactericidal for others.
What are the clinical indications?	Erythromycin (E-Mycin)—the prototype treating <i>Mycoplasma</i> and <i>Legionella</i> pneumonia and <i>Corynebacterium</i> infection. This drug is also effective against gram-positive organisms such as <i>Listeria</i> . Gram-negative organisms such as <i>Chlamydia</i> , <i>Helicobacter</i> , <i>Bordetella</i> , and <i>Neisseria</i> are also affected.
Is there a difference between erythromycin's antibacterial activity and that of clarithromycin and azithromycin?	The only major difference is that clarithromycin and azithromycin are more active against <i>Mycobacterium avium</i> complex and <i>Toxoplasma gondii</i> .
How does resistance to the macrolides develop?	Through at least two different mechanisms: <ol style="list-style-type: none"> 1. Defective uptake of the drug by the microbe 2. Bacterial plasmids coding for enzymes that inactivate these drugs
What is the route of administration?	Oral for all, plus IV for erythromycin and azithromycin
How are macrolides metabolized?	By the cytochrome P-450 system
Are there any adverse effects associated with the macrolides?	Yes—epigastric distress (nausea, vomiting, diarrhea) and cholestatic hepatitis
What are the drug-drug interactions?	Avoid using erythromycin with theophylline, oral anticoagulants, or cisapride; it will increase the serum concentrations of these drugs.

LINCOSAMIDES

What is lincomycin (Lincocin)?	An antibiotic elaborated by <i>Streptomyces lincolnensis</i> that resembles erythromycin
What is clindamycin (Cleocin)?	A chlorine derivative of lincomycin

How does clindamycin work?

This drug is a bacteriostatic agent that binds to the 50S ribosomal subunit and inhibits protein synthesis by interfering with aminoacyl translocation steps (see Figure 43-1).

What is the route of administration for clindamycin?

Oral

How is clindamycin metabolized?

Through both renal and hepatic routes

What is clindamycin's clinical use?

It is usually used to treat severe infections by anaerobic bacteria such as *Bacteroides fragilis*. Streptococci, staphylococci, and pneumococci are also inhibited. Clindamycin does not cover *Clostridium* or enterococci.

Does this drug readily enter the CNS?

No, but it does penetrate other body fluids well

What are the side effects?

Pseudomembranous colitis—
Lincosamides destroy the normal intestinal flora, which allows *Clostridium difficile* to grow and secrete its toxin, causing a bloody diarrhea. Treatment of this condition includes metronidazole or oral vancomycin.
Diarrhea
Granulocytopenia
Skin rashes

Quinolones and Drugs Used to Treat Urinary Tract Infections

QUINOLONES

List two members of this drug class.

1. Nalidixic acid
2. Cinoxacin

Why do the quinolones have limited use?

They are only useful as urinary antiseptics because they do not reach systemic bacteriacidal levels and because they rapidly develop resistance. They have largely been replaced by the fluoroquinolones.

FLUOROQUINOLONES

Name five drugs in this class.

1. Norfloxacin (Noroxin)
2. Levofloxacin (Levaquin)
3. Ciprofloxacin (Cipro)
4. Ofloxacin (Floxin)
5. Enoxacin (Penetrex)

There are many more; they can be recognized by the "ox" in their names.

What is the advantage of fluoroquinolones over quinolones?

The fluoroquinolones achieve a much higher concentration in the bloodstream and are therefore bactericidal against systemic organisms.

What is the pharmacologic mechanism of action of fluoroquinolones?

They inhibit DNA gyrase (topoisomerase II), thus blocking bacterial DNA synthesis.

Describe the distribution of the fluoroquinolones.

These drugs are well absorbed and widely distributed in body fluids, tissue, and bone, but not the CNS.

What is the activity of the fluoroquinolones?

They are broad-spectrum agents active against aerobic gram-negative bacteria (including *Pseudomonas* and *Legionella*) and many gram-positive organisms. Anaerobes are generally resistant.

What are the major uses of fluoroquinolones?

Urinary tract infections (UTIs)
Respiratory tract infections
Skin, bone, and soft tissue infections such as osteomyelitis
Prostatitis
Sexually transmitted diseases—
gonococcal and chlamydial infections
Diarrhea due to *Campylobacter*,
Salmonella, *Shigella* toxin, and
Escherichia coli

How are the fluoroquinolones eliminated?

Mainly by tubular secretion through the kidneys, although up to 20% can be metabolized by the liver

What are the adverse effects of fluoroquinolones?

CNS effects—headache, dizziness, insomnia
GI effects—diarrhea, nausea, abnormal liver function tests
Photosensitivity

Can fluoroquinolones be used in children?

No, because they cause cartilage erosion, which also rules out their use during pregnancy and nursing.

What is the route of administration of fluoroquinolones?

They can be administered IV or PO.

Does resistance develop against fluoroquinolones?

Yes, especially by *Staphylococcus*, *Pseudomonas*, and *Serratia*. Resistance develops through changes to the binding region of the fluoroquinolone target enzyme or because of a change in the penetration of the drug

Are there any important drug-drug interactions?

Yes—fluoroquinolones increase plasma theophylline levels.

URINARY ANTISEPTICS

NITROFURANTOIN (Furadantin)

What is nitrofurantoin?	An agent that is both bacteriostatic and bactericidal (at high doses) against gram-positive and gram-negative bacteria (except for <i>Proteus</i> and <i>Pseudomonas</i>)
What is its mechanism of action?	Nitrofurantoin alters various bacterial enzymes and bacterial DNA.
What is the clinical indication for nitrofurantoin?	UTI Especially those caused by <i>E. coli</i> and enterococci
What is the route of administration?	Oral
How is nitrofurantoin metabolized?	It is excreted into the urine through glomerular filtration.
What are the side effects?	Anorexia, nausea, and vomiting—most common effects Pulmonary infiltrates Hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency Neurological disorders such as polyneuropathies Chronic active hepatitis—rare but serious side effect Rashes Brown urine

METHENAMINE

How does methenamine work?	At a pH of 5.5 or less in the urine, it decomposes to formaldehyde, which kills most bacteria.
What is the clinical indication for this drug?	Chronic suppressive treatment of urinary tract infections, especially when the organism is <i>E. coli</i> .
What are the adverse effects?	GI distress Hematuria and albuminuria at higher doses

45

Folate Antagonists

What is the biologic role of folic acid?

It is an essential cofactor in purine, pyrimidine, and amino acid synthesis.

Can human cells absorb preformed folic acid?

Yes.

Can bacteria absorb preformed folic acid?

No! Bacteria must synthesize folic acid from pteridine and para-aminobenzoic acid (PABA). This is the basis for the selective toxicity of sulfonamides and trimethoprim.

SULFONAMIDES

Describe the structure of a sulfonamide compound.

It resembles PABA. (Fig 45-1)

How do sulfonamides work?

Because they resemble PABA, they bind and competitively **inhibit dihydropteroate synthetase**, the enzyme responsible for combining PABA and pteridine.

Give some examples of sulfonamides.

Sulfamethoxazole (Gantanol)
Sulfisoxazole (Gantrisin)
Sulfamethizole (Proklar)
Sulfasalazine (Azulfidine)
Sulfacetamide (Isopto Cetamide)
Silver sulfadiazine (Silvadene)
Mafenide (Sulfamylon)
Sulfadiazine

Are sulfonamides bactericidal?

No! They are bacteriostatic and therefore are most effective against rapidly growing organisms.

What is the clinical spectrum of sulfonamides?

Gram-positive and gram-negative organisms, including *Nocardia*, *Chlamydia*, *Escherichia coli*, *Klebsiella*, and *Enterobacter*.

What are the routes of administration and absorption for these drugs?

With few exceptions, all sulfa drugs are well absorbed after oral administration. Once absorbed they are largely bound to albumin. Sulfa drugs, in fact, will displace bilirubin and other drugs that were previously bound to albumin.

Do these drugs enter the CNS?

Yes! Sulfonamides easily penetrate the CNS, even in the absence of inflammation.

How are sulfonamides used clinically?

Sulfonamides are used to treat many different diseases, but they are most often used for the following (drugs of choice are indicated):

- Simple urinary tract infections due to *E. coli* and *Klebsiella* (they are not effective against *Pseudomonas*)—sulfisoxazole, sulfamethoxazole
- Ulcerative colitis—sulfasalazine (best because it is poorly absorbed)
- Burn infections—silver sulfadiazine
- Ocular infections, especially by *Chlamydia trachomatis*—sulfacetamide
- Nocardiosis—sulfisoxazole
- Toxoplasmosis—sulfadiazine in combination with pyrimethamine

Where are sulfonamides metabolized?

Sulfonamides are acetylated in the liver.

What toxicities should you watch for when prescribing sulfonamides to your patients?

- Hypersensitivity—rashes, exfoliative dermatitis, photosensitivity
- Stevens-Johnson syndrome
- Gastrointestinal effects—nausea and vomiting
- Hematotoxicity—Hemolytic anemia may occur in patients with glucose-6-phosphate dehydrogenase deficiency. Agranulocytosis and aplastic anemia have also been reported but are very rare.
- Crystalluria/hematuria—Adequate hydration and alkalinization of the urine prevents this problem, which is primarily seen with older sulfonamides such as sulfadiazine.

Kernicterus—In newborns, sulfonamides will displace bilirubin from albumin.

The excess bilirubin penetrates the CNS and causes this condition.

Phototoxicity

Remember the mnemonic

CRANK—Crystalluria,
Rashes, Anemia, Nausea,
Kernicterus.



Should pregnant women be given sulfonamides?

No! Sulfa drugs will cross into the placenta and breast milk, and therefore are contraindicated for pregnant and nursing women.

What drug interactions should you be particularly aware of when prescribing sulfonamides?

Patients who are also taking oral hypoglycemic agents or warfarin may experience a potentiation of effects from these drugs owing to displacement from serum albumin.

How does resistance to sulfonamides occur?

Resistance may occur in one of three ways:

1. Decreased intracellular accumulation of the drug
2. Increased production of PABA
3. A change in the sensitivity of dihydropteroate synthetase to the sulfonamides

TRIMETHOPRIM

How does it work?

Trimethoprim stops the conversion of dihydrofolate to tetrahydrofolate by inhibiting the enzyme **dihydrofolate reductase** (Figure 45-1).

What is the route of administration?

Oral

Is this drug commonly used alone?

No. Trimethoprim is most often combined with sulfamethoxazole; together, the two drugs are synergistic.

What can the trimethoprim/sulfamethizole combination drug (Bactrim, Septra) be used for?

The range of antibacterial spectrum and the clinical indications are larger than when a sulfonamide or trimethoprim is used alone. The most important uses include:

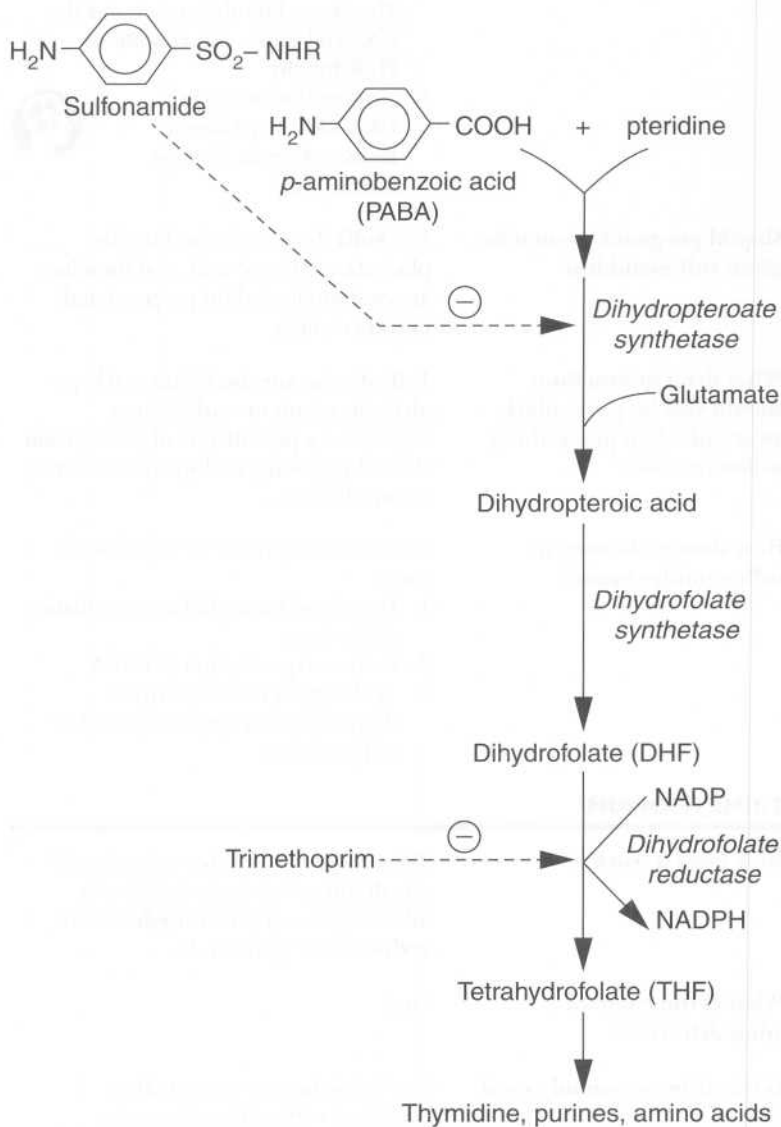


Figure 45-1. Action of folate inhibitors. (Redrawn from Gallia G, Hann CL, Hewson WH: *The Pharmacology Companion*. Alert & Oriented Publishing Company, 1997, p 176, Fig 5.3.)

Complicated or recurrent urinary tract infections (UTIs)

Bacterial prostatitis

Gonorrhea

Sinusitis/bronchitis

Acute otitis media

Pneumonia—drug of choice for pneumonia caused by *Pneumocystis carinii*; sometimes given in a nebulized or vaporized form

Toxoplasmosis

Can this drug be used for chancroid, shigellosis, typhoid fever (due to *Salmonella typhi*), and nocardiosis?

Yes! Bactrim is effective against all these infections.

What are the adverse effects of trimethoprim-sulfamethoxazole?

Dermatologic effects—rash, exfoliative dermatitis, urticaria. AIDS patients are especially susceptible to developing rashes.

Stevens-Johnson syndrome

Gastrointestinal effects—nausea, vomiting, glossitis, stomatitis

Hematologic effects—agranulocytosis, megaloblastic anemia (in folate-deficient patients), hemolytic anemia

Headache

Depression

Antifungal Drugs

What is the structure of a fungus?

Fungi are eukaryotic organisms with rigid cell walls that contain chitin as well as polysaccharides.

What is a mycosis?

An infectious disease caused by a fungus. The infections can be systemic or superficial in nature.

SYSTEMIC AND SUBCUTANEOUS MYCOSES

Name five drugs used for systemic and subcutaneous mycoses.

1. Amphotericin B (Fungizone)
2. Flucytosine (Ancobon)
3. Ketoconazole (Nizoral)
4. Fluconazole (Diflucan)
5. Itraconazole (Sporanox)

AMPHOTERICIN B

What is the classification of this drug?

Amphotericin B is a polyene antibiotic.

What is its importance?

It is the drug of choice for treating systemic mycotic infections.

How does this drug work?

Fungal cells contain ergosterol, a sterol specific to fungal cell membranes. Amphotericin B binds to ergosterol and forms pores or channels within the membrane. This allows electrolytes to leak from the cell, which results in cell death (Figure 46-1).

Does amphotericin B bind to cholesterol?

No. Only ergosterol is affected by this drug.

Does amphotericin B enter the CNS?

No

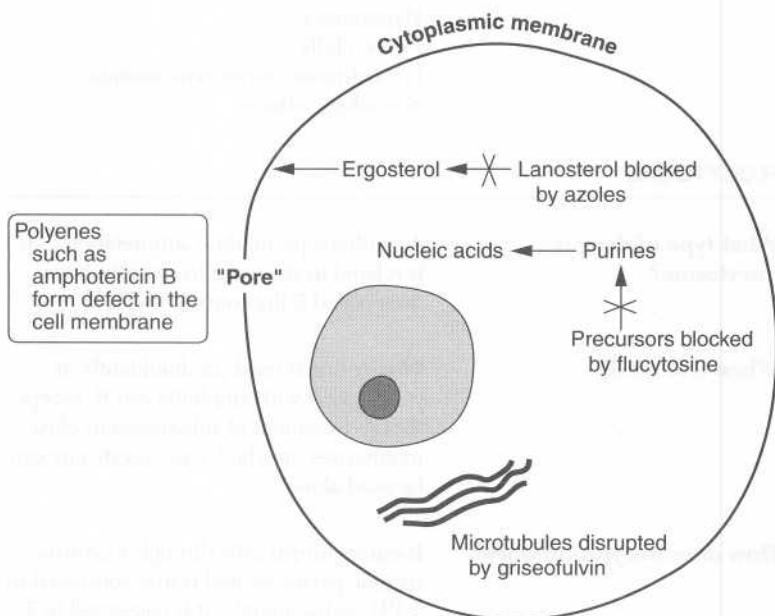


Figure 46–1. Sites of action of antifungal drugs.

What is this drug's anti-fungal spectrum?

Amphotericin B is effective against:

Candida

Histoplasma capsulatum

Cryptococcus neoformans

Blastomyces dermatitidis

Aspergillus

Coccidioides immitis

What is the route of administration?

Usually intravenous; however, for fungal meningitis intrathecal administration is required.

What are its pharmacokinetics?

Amphotericin B is poorly absorbed from the gastrointestinal tract. Bile is the major route of excretion. A small part of the drug, however, is eliminated in the urine.

What are adverse signs to watch for during administration?

Renal impairment—80% of patients exhibit decreased glomerular filtration rate and changes in renal tubular function.

Hypotension
Fever, chills
Hypochromic normocytic anemia
Neurologic effects

FLUCYTOSINE

What type of drug is flucytosine?

A synthetic pyrimidine antimetabolite. It is related in structure to an anticancer drug called 5-fluorouracil (5-FU).

When is it used?

Flucytosine is used predominantly in conjunction with amphotericin B, except for the treatment of subcutaneous chromomycoses, in which case flucytosine can be used alone.

How does flucytosine work?

It enters fungal cells through a cytosine-specific permease and is first converted to 5-FU. Subsequently, it is converted to 5-fluorodeoxyuridine monophosphate (5-FdUMP). This acid inhibits thymidylate synthetase, which is an essential enzyme in the production of DNA (Figure 46-2). Mammalian cells do not convert flucytosine to 5-FU.

Is its antifungal spectrum broad or narrow?

Narrow; it only affects the following:
Candida
Cryptococcus neoformans
Aspergillus
Agents causing chromomycosis

How is flucytosine usually administered?

Orally

What are the pharmacokinetics of flucytosine?

Flucytosine distributes well throughout the tissues, including the CSF. It is excreted intact in the urine.

What are the toxicities of this drug?

Hematologic—reversible bone marrow depression leading to neutropenia and thrombocytopenia
Elevated hepatic enzymes
Gastrointestinal disturbances—nausea, vomiting, enterocolitis

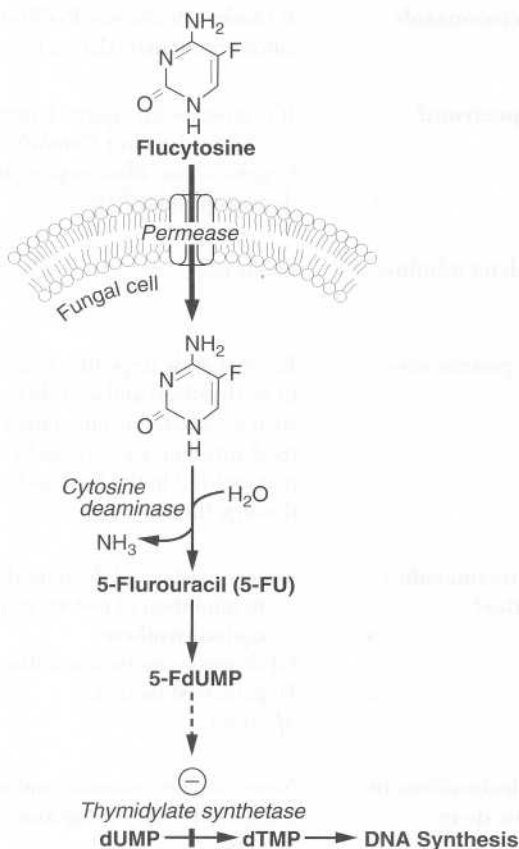


Figure 46–2. Mode of action of flucytosine. 5-FdUMP = 5-fluorodeoxyuridylic acid. dUMP = deoxyuridine monophosphate; dTMP = deoxythymidine monophosphate. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 339.)

KETOCONAZOLE

Into what category does this drug fit?

Ketoconazole is an azole, along with fluconazole, itraconazole, miconazole, clotrimazole, and econazole.

They all have the same mechanism of action but different therapeutic indications. Their development provided a way to treat systemic infections orally.

How does ketoconazole work?	It blocks cytochrome P-450-mediated lanosterol demethylation to ergosterol.
What is its spectrum?	It is most useful against <i>Histoplasma</i> but can be used against <i>Candida</i> , <i>Cryptococcus</i> , <i>Blastomyces</i> , and dermatophytes.
How is this drug administered?	Orally only
What are its pharmacokinetics?	Ketoconazole depends on gastric acidity to be dissolved and absorbed; drugs such as cimetidine and antacids impair its absorption. Ketoconazole is metabolized in the liver and excreted through the bile.
What are ketoconazole's major toxicities?	Gynecomastia and decreased libido due to inhibition of testosterone and cortisol synthesis GI distress—nausea, vomiting Hepatic dysfunction Allergies
State contraindications to the use of this drug.	Never use ketoconazole and amphotericin B together—they antagonize each other's actions.

FLUCONAZOLE

What are the major advantages of fluconazole over ketoconazole?	Fluconazole can enter the CSF in high concentrations and is not dependent on acidic pH for absorption.
What are the therapeutic uses of fluconazole?	Coccidioidal meningitis—drug of choice Disseminated histoplasmosis Oral and esophageal candidiasis Prevention of relapse of cryptococcal meningitis in AIDS patients whose infection has been controlled by amphotericin B
What toxicities are associated with ketoconazole?	Nausea and vomiting Headache Skin rash

ITRACONAZOLE

What is itraconazole's therapeutic use?	Subcutaneous chromomycosis (blastomycosis)—drug of choice Histoplasmosis Cutaneous sporotrichosis <i>Candida</i> infections Tinea
What are the adverse effects of itraconazole?	GI distress, hypertriglyceridemia, and hypokalemia

SUPERFICIAL MYCOSES

Identify five major drugs used to treat superficial mycotic infections.	1. Griseofulvin (Fulvicin) 2. Nystatin (Mycostatin) 3. Miconazole (Monistat) 4. Clotrimazole (Canesten cream) 5. Econazole (Spectazole)
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GRISEOFULVIN

What is its mode of action?	Griseofulvin enters susceptible fungal cells and inhibits microtubule function (see Figure 46-1). With long-term therapy (weeks to months), this drug accumulates in the newly synthesized stratum corneum, making these cells undesirable for fungal growth.
What is the antifungal spectrum of this drug?	It is effective only against dermatophytes, including <i>Trichophyton</i> , <i>Microsporum</i> , and <i>Epidermophyton</i> .
What are the pharmacokinetics of this drug?	Griseofulvin is absorbed well orally, especially with a high-fat diet, and distributed to the keratin-containing stratum corneum. It is eliminated through the bile.
State this drug's adverse effects.	Headache Hepatotoxicity GI irritation

NYSTATIN

What is the structure of drug?	Nystatin is a polyene similar in structure to amphotericin B, with the same mechanism of action.
What is the route of administration?	Topical

What is nystatin's therapeutic use?	Treatment of local <i>Candida</i> infections
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MICONAZOLE, CLOTRIMAZOLE, AND ECONAZOLE

What is the route of administration for these drugs?	Topical. They are highly toxic if used systemically.
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What are the indications for use?	Superficial infections of the skin and mucous membranes
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What are the pharmacologic properties of these drugs?	They are very similar to ketoconazole in mechanism of action, spectrum, and distribution.
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Antiprotozoal Drugs

What are protozoa?

Unicellular organisms that commonly live a parasitic existence.

MALARIA

Which organism causes malaria?

Plasmodium species

Which plasmodium species infect humans?

P. falciparum

P. malariae

P. ovale

P. vivax

What is the vector of transmission?

The female *Anopheles* mosquito

How are antimalarial drugs differentiated?

By the stage in the *Plasmodium* life cycle in which they are effective

What are the five stages in the *Plasmodium* life cycle?

1. A carrier mosquito injects the sporozoite into a human.
2. The sporozoite is transformed into a merozoite in the liver.
3. The merozoite enters into the bloodstream and parasitizes the erythrocytes. (At this stage, the organism is known as a blood schizont.)
4. Erythrocyte lysis occurs with release of gametocytes.
5. A non-carrier mosquito ingests gametocytes by biting an infected human.

Refer to Figure 47–1.

Which *Plasmodium* species have a dormant hepatic (hypnozoite) stage that causes recurrent infections and relapses?

P. ovale and *P. vivax*

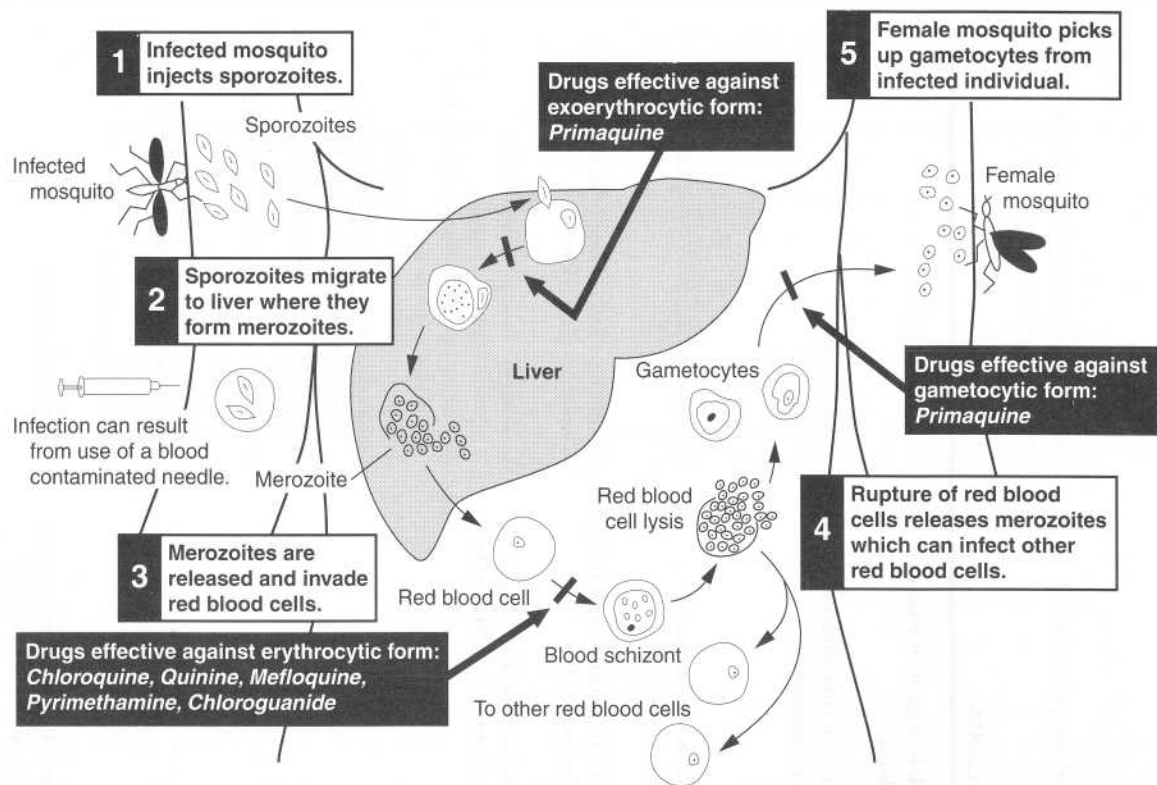


Figure 47-1. Life cycle of the malarial parasite showing the sites of action of antimalarial drugs. (Redrawn from Mycek M], Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: *Lippincott's Illustrated Reviews: Pharmacology*, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 350.)

What drugs are used to treat malaria?

Chloroquine (Aralen)
Quinine (Quinamm)
Mefloquine (Lariam)
Pyrimethamine (Daraprim)
Pyrimethamine/sulfadoxine (Fansidar)
Chloroguanide (Paludrine)
Primaquine

CHLOROQUINE (Aralen)

How does chloroquine work?

The mechanism of action is not known for certain, but it may include:

- Interfering with DNA and RNA synthesis
- Raising the pH of plasmodia vacuoles, which prevents the parasite from metabolizing red blood cell hemoglobin
- Blockade of plasmodial heme polymerase which leads to accumulation of toxic hemoglobin breakdown products

What is the route of administration?

Oral

How is chloroquine distributed?

It penetrates the CNS and crosses the placenta. It concentrates in erythrocytes, liver, spleen, kidney, lung, leukocytes, and melanin-containing tissues.

How is chloroquine metabolized?

It is rapidly and completely absorbed, and extensively dealkylated by the mixed-function oxidases.

What is its major clinical use?

It is used for acute attacks of malaria. Because chloroquine is a blood schizonticide, it will not eradicate hypnozoites and is therefore not useful for the treatment of relapsing malaria caused by *P. ovale* or *P. vivax*.

What other use does this drug have?

Chloroquine has anti-inflammatory effects and is sometimes used in autoimmune disorders.

What are chloroquine's adverse effects?

Low dose—GI upset, headache, rash (should not be used in patients with psoriasis or porphyria)

High dose—peripheral neuropathies, myocardial depression with ECG changes, retinal damage (requires routine ophthalmologic examinations), auditory impairment, and toxic psychosis

Long-term treatment—discoloration of the nail beds and mucous membranes; hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency

QUININE (Quinamm)

How does this drug work?

Quinine is a blood schizonticide that forms complexes with double-stranded DNA and prevents strand separation.

What is its route of administration?

Oral

How is quinine metabolized?

It is excreted renally.

What is this drug's clinical use?

It is used on chloroquine-resistant malaria-causing species (usually in combination with pyrimethamine and a sulfonamide).

What are its adverse effects?

Cinchonism—nausea, vomiting, tinnitus, vertigo, headache, and blurred vision
Hemolytic anemia in G-6-PD-deficient patients

What is a rare complication that can occur in patients who have been sensitized to quinine?

Blackwater fever, in which massive red blood cell lysis leads to hemoglobinuria, which causes dark urine and renal failure. It is potentially fatal.

MEFLOQUINE (Lariam)

How does this drug work?

Mefloquine is a blood schizonticide with an unknown mechanism of action.

What is the route of administration?

Oral

How is mefloquine distributed?	It concentrates in the liver and the lungs.
How is it metabolized?	It has a long half-life (17 days) owing to extensive enterohepatic recirculation and binding to tissue and plasma proteins. It is excreted in the feces.
What is this drug's clinical use?	It is used in prophylaxis and treatment of chloroquine-resistant <i>P. falciparum</i> .
What are its adverse effects?	It is less toxic than quinine. However, it may cause nausea, vomiting, and dizziness; at high doses it may cause seizures, hallucinations, and depression.

PYRIMETHAMINE (Daraprim)

How does this drug work?	Pyrimethamine is a blood schizonticide that selectively inhibits plasmodial dihydrofolate reductase, thereby depriving the organism of tetrahydrofolate, a cofactor in the biosynthesis of purines and pyrimidines. Pyrimethamine can be combined with sulfadoxine to produce synergistic effects.
What is its route of administration?	Oral
How is this drug metabolized?	It is excreted in the urine after partial metabolism.
What is its clinical use?	When combined with sulfadiazine, this drug is the treatment of choice for toxoplasmosis. It is mostly active against <i>P. falciparum</i> .
What are the adverse effects?	Folic acid deficiency in high doses Rash GI distress Hemolysis Renal damage

PYRIMETHAMINE/SULFADOXINE (Fansidar)

What is Fansidar's clinical use?	This combination agent is used against chloroquine-resistant species owing to its sequential blockade of two steps in folic acid synthesis.
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CHLOROQUANIDE (Paludrine)

How does this drug work?	Chloroguanide is a blood schizonticide whose active form (cycloguanil) is a selective inhibitor of protozoan dihydrofolate reductase.
What is its route of administration?	Oral
How is it metabolized?	It has a shorter half-life than other antifolates (12–14 hours). It is excreted in the urine.
What is chloroguanide's clinical use?	Prophylaxis and suppression of malaria. This drug's use is limited owing to the rapid emergence of resistant strains.
Are there any adverse effects?	Rash GI distress Hemolysis Renal damage

PRIMAQUINE

How does this drug work?	Primaquine is a tissue schizonticide and gametocide that forms redox compounds which act as cellular oxidants.
What is its route of administration?	It is administered orally.
How is the drug metabolized?	It undergoes rapid oxidative biotransformation. Metabolites exert the schizonticidal effect and are excreted in the urine.
What is its clinical use?	Primaquine is used to treat relapsing malaria; it eradicates the liver stages of <i>P. vivax</i> and <i>P. ovale</i> (primary as well as secondary exoerythrocytic forms). It is also gametocidal for all four <i>Plasmodium</i> species and can therefore be used to interrupt transmission of the disease.
Is primaquine effective in treating acute attacks?	No; therefore, it must be used in conjunction with a blood schizonticide such as chloroquine.

What are its adverse effects?	Methemoglobinemia GI distress Headaches Pruritus Hemolytic anemia in G-6-PD deficiency Granulocytopenia Agranulocytosis (rare)
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TOXOPLASMOSIS

What organism causes Toxoplasmosis?	<i>Toxoplasma gondii</i>
How is it transmitted to humans?	Ingestion of raw or undercooked infected meat Shedding of infectious oocysts by cats Transplacentally
What is the treatment of choice?	Pyrimethamine in combination with sulfadiazine

LEISHMANIASIS

Which organism causes leishmaniasis?	<i>Leishmania</i>
What is the vector of transmission?	Infected sandflies
What is the life cycle of <i>Leishmania</i>?	<ol style="list-style-type: none"> 1. A sandfly transfers the flagellated promastigote from an infected animal or human to an uninfected one. 2. The promastigote is phagocytized by macrophages. 3. In the macrophage, the promastigote changes to a nonflagellated amastigote and multiplies, killing the cell. 4. The released amastigotes are phagocytized, and the cycle continues.
What is the drug of choice for the treatment of both mucocutaneous and visceral leishmaniasis?	Sodium stibogluconate (Pentostam)
How does this drug work?	Through inhibition of glycolysis at the phosphofructokinase reaction

What is its route of administration?	Parenteral (it is not absorbed orally)
How is this drug metabolized?	There is minimal metabolism, and it is excreted in the urine.
What are its adverse effects?	Pain at the injection site GI distress Cardiac arrhythmias
Which laboratory tests must be ordered during treatment?	Tests to monitor renal and hepatic function
What are alternative agents for the treatment of leishmaniasis?	Pentamidine—visceral leishmaniasis Metronidazole (Flagyl)—cutaneous lesions Amphotericin B—mucocutaneous leishmaniasis

TRYPANOSOMIASIS

Which organisms cause trypanosomiasis?	<i>Trypanosoma cruzi</i> —American sleeping sickness (Chagas' disease) <i>T. brucei</i> (subspecies <i>gambiense</i> and <i>rhodesiense</i>)—African sleeping sickness
What drugs are used to treat trypanosomiasis?	Melarsoprol (Mel B) Pentamidine (Pentam) Nifurtimox (Lampit) Suramin (Antrypol)

MELARSOPROL (Mel B)

How does this drug work?	Melarsoprol inhibits sulfhydryl groups in parasitic enzymes.
What is the route of administration?	IV or oral
How is it distributed?	Into the CNS
What is its metabolism?	It is oxidized by the host to a nontoxic compound. It has a very short half-life and is rapidly excreted in the urine.

What is its clinical use?	It is the drug of choice for the treatment of African sleeping sickness with CNS involvement.
What are the adverse effects?	Encephalopathy GI distress (avoided if patient is fasting during administration) Hypersensitivity reactions Hemolytic anemia in G-6-PD-deficient patients
Are there any contraindications to the use of melarsoprol?	It cannot be used in patients who have influenza.

PENTAMIDINE (Pentam)

How does this drug work?	The mechanism of action is unknown. Pentamidine is concentrated in <i>T. brucei</i> by a high-affinity uptake system, and the drug is thought to either bind to the organism's DNA or inhibit glycolysis.
What is its route of administration?	IM or aerosol. IV administration may lead to hypotension and tachycardia.
How is pentamidine distributed?	It <i>does not</i> enter the CNS, but is concentrated in the liver and kidneys.
What is its metabolism?	This drug has a 2- to 4-week half-life and is excreted unchanged in the urine.
What is the major clinical use for pentamidine?	It is the drug of choice for hemolympathic stages of African sleeping sickness (not effective for the CNS stage).
For what other condition is this drug used?	The aerosol form is used for prophylaxis and treatment of <i>Pneumocystis carinii</i> pneumonia that is refractory to trimethoprim-sulfamethoxazole.
List the adverse effects.	Reversible nephrotoxicity Respiratory stimulation followed by depression Pancreatic cell dysfunction

NIFURTIMOX (Lampit)

How does this drug work?	Nifurtimox forms intracellular oxygen radicals which are toxic to the organism.
What is the route of administration?	Oral
How is nifurtimox metabolized?	It is rapidly absorbed and metabolized; by-products are renally excreted.
What is this drug's clinical use?	It is the drug of choice for American sleeping sickness (Chagas' disease), and it is also effective for mucocutaneous leishmaniasis.
Does Nifurtimox cure Chagas' disease?	No! It is suppressive, not curative.
What are the adverse effects?	Anaphylaxis Dermatitis and icterus GI irritation Peripheral neuropathy CNS disturbances Suppression of cell-mediated immunity

SURAMIN (Antrypol)

How does this drug work?	Through inhibition of enzymes involved in energy metabolism
What is the route of administration?	IV
What are suramin's clinical uses?	Prophylaxis and treatment of early stages (without CNS involvement) of African sleeping sickness Drug of choice for treating infection by <i>Onchocerca volvulus</i> , in combination with diethylcarbamazine
What are the adverse effects?	Albuminuria Rash GI distress—nausea and vomiting Urticaria Neurologic complications—paresthesias, photophobia, palpebral edema, hyperesthesia Shock

Are there any indications to discontinue the drug?

Yes—renal casts in the urine

AMEBIASIS

What organism causes amebiasis (amebic dysentery)?

Entamoeba histolytica

Describe the six stages of this organism's life cycle.

1. Ingestion of cysts
2. Formation of trophozoites in the intestinal lumen
3. Trophozoite penetration into the intestinal wall
4. Trophozoite multiplication within the colonic wall
5. Systemic invasion
6. Infective cysts expelled in feces

Refer to Figure 47-2.

How are amebicides classified?

Mixed—effective against luminal and systemic disease

Luminal—effective only in the bowel lumen

Systemic—effective in the intestine and liver

Which amebicides are mixed?

Metronidazole (Flagyl)

Which amebicides are luminal?

Diloxanide furoate (Furamide)
Paromomycin (Humatin)
Iodoquinol (Diodoquin)
Tetracycline

Which amebicides are systemic?

Emetine
Dehydroemetine
Chloroquine (Aralen)

METRONIDAZOLE (Flagyl)

What action does this drug have?

Metronidazole is selectively toxic to amebae, anaerobes and anoxic/hypoxic cells.

How does this drug work?

Metronidazole has a nitro group that receives electrons from ferredoxin (present in anaerobic parasites) in a redox reaction. The resultant compound binds both to proteins and DNA and is cytotoxic.

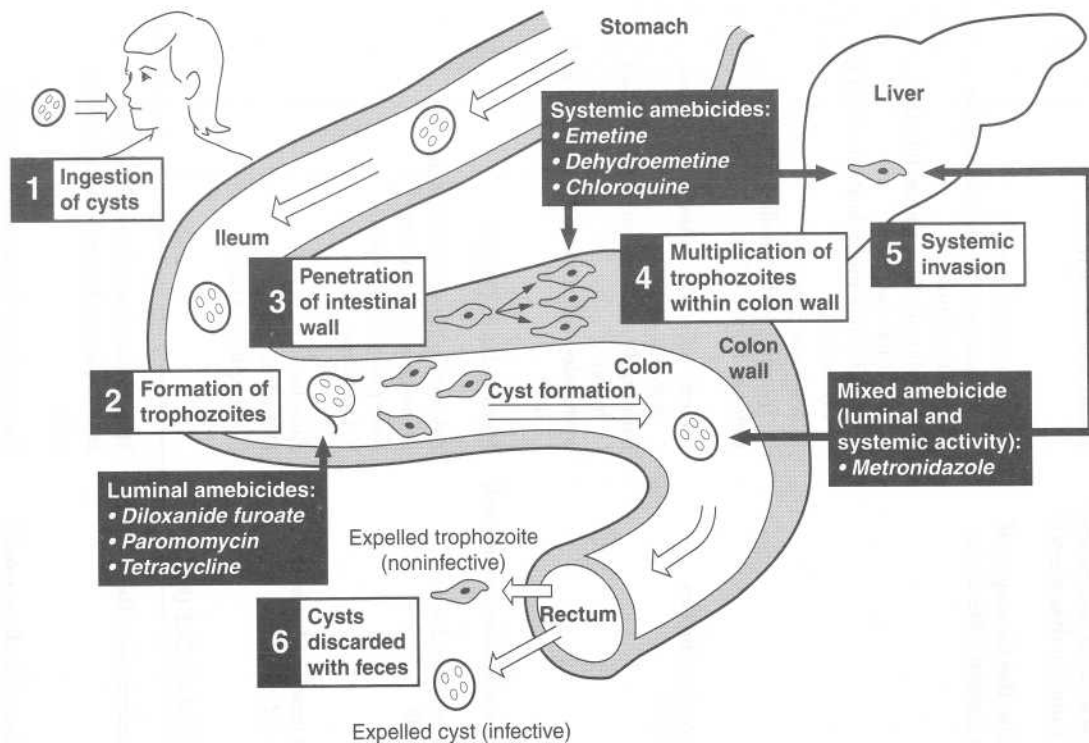


Figure 47-2. Life cycle of *Entamoeba histolytica* showing sites of action of amebicidal drugs. (Redrawn from Mycek MJ, Gertner SB, Perper MM [Harvey RA, Champe PC, eds]: Lippincott's Illustrated Reviews: Pharmacology, 2nd ed. Philadelphia, Lippincott-Raven Publishers, 1997, p 346.)

What is the route of administration?	Oral or IV
What is the distribution of metronidazole?	It is widely distributed throughout tissues and fluids, including seminal and vaginal fluids, saliva, and CSF.
How is metronidazole metabolized?	By hepatic oxidation and glucuronidation. Its rate of metabolism is increased when the drug is given with agents that induce hepatic metabolism (such as phenobarbital).
What is this drug's major clinical use?	It is the drug of choice for infections caused by <i>E. histolytica</i> (usually with a luminal amebicide such as diloxanide furoate), <i>Giardia lamblia</i> , and <i>Trichomonas vaginalis</i> .
Are there other clinical uses?	Metronidazole is also used for infections caused by <i>Gardnerella vaginalis</i> , <i>Bacteroides fragilis</i> , and <i>Clostridium difficile</i> .
What are the adverse effects?	<ul style="list-style-type: none"> Disulfiram-like reaction with ethanol GI irritation—cramps, nausea, and vomiting Metallic taste Potential of warfarin's (Coumadin's) anticoagulation effects Discoloration of urine Oral moniliasis CNS disturbances—dizziness, vertigo, numbness, and paresthesias
Is metronidazole safe for pregnant women?	No! Metronidazole is teratogenic and should be avoided in pregnant women and nursing mothers.

DILOXANIDE FUROATE (Furamide)

How does this drug work?	The mechanism of action is unknown.
What is the route of administration?	Oral

How is diloxanide metabolized? It is hydrolyzed in the intestinal mucosa, and 90% is absorbed; the **unabsorbed** drug is the active agent. Metabolites appear in the urine.

What is the clinical use? It is the drug of choice for asymptomatic cyst shedders. It is also used in combination with metronidazole for treating luminal amebiasis due to *E. histolytica*.

What are this drug's adverse effects? Flatulence
Dry mouth
Pruritus
Urticaria

Are there any contraindications to the use of diloxanide furoate? It is contraindicated in pregnant women and in children younger than 2 years of age.

PAROMOMYCIN (Humatin)

How does this drug work? Paromomycin is an aminoglycoside antibiotic that causes protozoal cell membrane leakage. It also reduces the population of intestinal flora, which is a food source for the amebae.

What is the route of administration? Oral. Because this drug is not significantly absorbed from the GI tract, it only exhibits luminal effectiveness.

What is this drug's clinical use? Treatment of luminal amebiasis

What are the adverse effects? GI distress and diarrhea. Systemic absorption may result in headaches, dizziness, rash, and arthralgias.

IDOQUINOL (Diodoquin)

What is this drug's mechanism of action? It is unknown.

What is it used for? Asymptomatic amebiasis

What are its toxicities? Headache
Fever
Diarrhea, nausea, and vomiting

TETRACYCLINE

How does this drug work?	Tetracycline is an antibiotic that eliminates the normal intestinal flora and therefore the ameba's main food source; it is not a direct amebicide.
What is the route of administration?	Oral
What substances decrease absorption?	Dairy foods and antacids that contain magnesium and aluminum, because they form nonabsorbable chelates with the drug
Are there any contraindications to the use of tetracycline?	Yes—it is contraindicated in children younger than 8 years of age and in pregnant women.
What is the clinical use for this drug?	Tetracycline is not highly effective when used alone; it is used mainly as an adjunct to other amebicides.

EMETINE AND DEHYDROEMETINE

How do these drugs work?	They inhibit protein synthesis by blocking ribosomal movement along mRNA.
Describe their distribution	They are distributed widely to tissues.
How are they metabolized?	By slow renal excretion
What is the clinical use?	Because of their severe toxicity, emetine and dehydroemetine are used only as backup treatment for severe intestinal or hepatic amebiasis in hospitalized patients.
What are the adverse effects?	<p>Cardiotoxicity—arrhythmias, congestive heart failure</p> <p>Neuromuscular weakness</p> <p>Nausea</p> <p>Dizziness</p> <p>Rash</p> <p>Pain at injection site</p>

CHLOROQUINE (Aralen)

What is this antimalarial drug's clinical use as it relates to amebiasis?	Treatment and prevention of amebic liver abscesses in conjunction with metronidazole and diloxanide furoate
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Anthelmintic Drugs

What is a helminth?

Helminth is a Greek word meaning worm.

What are the classifications of helminths?

There are three classifications:

1. Nematodes (roundworms)
2. Trematodes (flukes)
3. Cestodes (tapeworms)

The last two are types of flatworms.

Name six drugs used predominantly in the treatment of nematodes.

1. Mebendazole (Vermox)
2. Thiabendazole (Mintezol)
3. Albendazole (Zentel)
4. Pyrantel pamoate (Antiminth)
5. Diethylcarbamazine (Hetrazan)
6. Ivermectin (Mectizan)

Refer to Table 48-1.

Name two drugs used predominantly in the treatment of cestodes and trematodes.

1. Praziquantel
2. Niclosamide

Refer to Table 48-1.

ANTHELMINTICS FOR NEMATODES

MEBENDAZOLE (Vermox)

What infections are treated with mebendazole?

Mebendazole is the drug of choice for pinworm (*Enterobius vermicularis*) and whipworm (*Trichuris trichiura*). It is also very effective against *Necator americanus* (hookworm) and *Ascaris lumbricoides* (roundworm).

What is the mechanism of action?

Mebendazole interferes with the synthesis of parasite microtubules and decreases glucose uptake.

What is the route of administration?

Oral. Very little of the drug is absorbed systemically.

Table 48–1. Drugs for the Treatment of Helminthic Infections.

Infesting Organism	Drug of Choice	Alternative Drugs
Roundworms (nematodes)		
<i>Ascaris lumbricoides</i> (roundworm)	Pyrantel pamoate or mebendazole	Albendazole, ² piperazine, or levamisole ²
<i>Trichuris trichiura</i> (whipworm)	Mebendazole	Albendazole ² or oxantel/pyrantel pamoate ¹
<i>Necator americanus</i> (hookworm); <i>Ancylostoma duodenale</i> (hookworm)	Pyrantel pamoate ² or mebendazole	Albendazole ² or levamisole ²
Combined infection with <i>Ascaris</i> , <i>Trichuris</i> , and hookworm	Mebendazole or albendazole ²	Oxantel/pyrantel pamoate ¹
Combined infection with <i>Ascaris</i> and hookworm	Mebendazole or pyrantel pamoate ²	Albendazole ²
<i>Strongyloides stercoralis</i> (threadworm)	Ivermectin ³	Thiabendazole, albendazole ^{2,4}
<i>Enterobius vermicularis</i> (pinworm)	Mebendazole or pyrantel pamoate	Albendazole ²
<i>Trichinella spiralis</i> (trichinosis)	Mebendazole ^{2,4} or thiabendazole ⁴ ; add corticosteroids for severe infection	Albendazole ^{4,5} ; add corticosteroids for severe infection
Cutaneous larva migrans (creeping eruption)	Albendazole ⁵ or ivermectin ²	Thiabendazole
Visceral larva migrans	Thiabendazole ⁸ or albendazole ²	Mebendazole ^{2,4} or ivermectin ⁴
<i>Angiostrongylus cantonensis</i>	Levamisole ^{2,4} or thiabendazole ⁴	Albendazole ^{2,4} or mebendazole ^{2,4}
<i>Wuchereria bancrofti</i> (filariasis); <i>Brugia malayi</i> (filariasis); tropical eosinophilia; <i>Loa loa</i> (loiasis)	Diethylcarbamazine ⁶	Ivermectin ^{3,7}
<i>Onchocerca volvulus</i> (onchocerciasis)	Ivermectin	Suramin ⁷
<i>Dracunculus medinensis</i> (guinea worm)	Metronidazole ²	Thiabendazole ² or mebendazole ²

continued

Table 48–1. Drugs for the Treatment of Helminthic Infections.

Infesting Organism	Drug of Choice	Alternative Drugs
Flukes (trematodes)		
<i>Schistosoma haematobium</i> (bilharziasis)	Praziquantel	Metrifonate ¹
<i>Schistosoma mansoni</i>	Praziquantel	Oxamniquine
<i>Schistosoma japonicum</i>	Praziquantel	
<i>Clonorchis sinensis</i> (liver fluke); <i>Opisthorchis</i> species	Praziquantel ²	Albendazole ^{2,4} or mebendazole ^{2,4}
<i>Paragonimus westermani</i> (lung fluke)	Praziquantel ²	Bithionol ⁷
<i>Fasciola hepatica</i> (sheep liver fluke)	Bithionol ⁷ or triclabendazole ^{1,4,9}	Praziquantel ^{2,8} or emetine or dehydro-emetine ⁷
<i>Fasciolopsis buski</i> (large intestinal fluke)	Praziquantel ² or niclosamide ²	Tetrachloroethylene ¹
<i>Heterophyes heterophyes</i> ; <i>Metagonimus yokogawai</i> (small intestinal flukes)	Praziquantel ² or niclosamide ²	Tetrachloroethylene ¹
Tapeworms (cestodes)		
<i>Taenia saginata</i> (beef tapeworm)	Niclosamide or praziquantel ²	Mebendazole ^{2,4}
<i>Diphyllobothrium latum</i> (fish tapeworm)	Niclosamide or praziquantel ²	

<i>Taenia solium</i> (pork tapeworm)	Niclosamide or praziquantel ²	
Cysticercosis (pork tapeworm larval stage)	Albendazole	Praziquantel ²
<i>Hymenolepis nana</i> (dwarf tapeworm)	Praziquantel ²	Niclosamide
<i>Hymenolepis diminuta</i> (rat tapeworm); <i>Dipylidium caninum</i>	Niclosamide or praziquantel ²	
<i>Echinococcus granulosus</i> (hydatid disease); <i>Echinococcus multilocularis</i>	Albendazole	Mebendazole ^{2,8}

¹Not available in the USA but available in some other countries

²Available in the USA but not labeled for this indication

³Available in the USA from Merck Sharpe & Dohme

⁴Effectiveness not established

⁵Available in the USA

⁶Available in the USA from Wyeth-Ayerst Laboratories

⁷Available in the USA only from the Parasitic Disease Drug Service, Parasitic Diseases Branch, Centers for Disease Control and Prevention, Atlanta

⁸Effectiveness is low

⁹A veterinary drug, not approved for human use

(Adapted from Katzung BG: *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT, Appleton & Lange, 1998, p 863–864.)

Is mebendazole safe for pregnant women?

No! The drug has proved teratogenic in animal experiments, so it should not be given to pregnant women. In general, most anthelmintic drugs are not considered safe in pregnancy.

What are the adverse effects of mebendazole?

Adverse effects are usually mild. The most frequent complaints are GI disturbances such as nausea and vomiting. Intrahepatic cholestasis has also been reported.

THIABENDAZOLE (Mintezol)

What is this drug's mechanism of action?

Thiabendazole, like mebendazole, binds to tubulin and inhibits microtubule polymerization.

What is the route of administration?

Oral, as is the case for most of the anthelmintics

What is its therapeutic use?

Thiabendazole can be used for treatment of the following infections:
Strongyloides stercoralis (threadworm)
 Cutaneous larva migrans caused by *Ancylostoma* species
 Visceral larva migrans caused by *Toxocara*

What are the adverse effects of this drug?

The most important side effects of thiabendazole are:
 CNS effects—tingling and numbness
 GI effects—diarrhea, nausea,
 Reactions caused by dying parasites—fever, chills, and lymphadenopathy, Stevens-Johnson syndrome (rare)

ALBENDAZOLE (Zentel)

What is this drug?

A relatively new broad-spectrum anthelmintic which, along with mebendazole and thiabendazole, belongs to a family of drugs known as benzimidazoles.

What is albendazole's clinical use?

In the United States it is primarily used for cysticercosis and hydatid disease.

How does it work?

Albendazole blocks glucose uptake, resulting in eventual depletion of the parasites' energy stores.

What are the adverse effects of albendazole?

The adverse effects are mild and include nausea, vomiting, and dizziness.

PYRANTEL PAMOATE (Antiminth)

What is this drug's therapeutic use?

Pyrantel pamoate is the drug of choice for treating *Ascaris* infections; it also can be used for pinworms and hookworms.

How does it work?

Pyrantel pamoate acts as a depolarizing neuromuscular blocking agent that causes persistent activation of nicotinic receptors and thus paralysis of the worm.

What is the toxicity?

Toxic effects are usually transient and may include nausea, vomiting, headache, and rash.

DIETHYLCARBAMAZINE (Hetrazan)

What are the clinical indications for this drug?

Diethylcarbamazine is the drug of choice for the treatment of filariasis caused by *Wuchereria bancrofti*. It is also used as an alternative in the treatment of onchocerciasis.

What is its mechanism of action?

The precise mechanism is unknown; diethylcarbamazine is thought to decrease the muscular activity of the parasites.

What are the adverse effects?

Toxic effects are usually mild, but may include headache, nausea, and vomiting. The Mazzotti reaction may occur in patients receiving treatment for onchocerciasis. This reaction occurs as a result of the effects of dying parasites and is characterized by pruritus, lymphadenopathy, hypotension, and tachycardia.

IVERMECTIN (Mectizan)

What is this drug's therapeutic use?

Ivermectin is the drug of choice for river blindness caused by *Onchocerca volvulus* and for strongyloidiasis caused by *Strongyloides stercoralis* (threadworm).

How does it work?

The drug intensifies GABA-mediated neurotransmission in nematodes and causes immobilization of parasites.

Does ivermectin affect human GABA receptors?

No. In humans GABA receptors are located only in the brain, and ivermectin does not cross the blood-brain barrier.

What toxicities should you watch for?

Fever, headache, dizziness, and pruritus. These symptoms are usually of short duration and can be controlled.

ANTHELMINTICS FOR TREMATODES AND CESTODES

PRAZIQUANTEL (Biltricide)

What is this drug's therapeutic use?

Praziquantel is the drug of choice for treatment of schistosomiasis (all species), certain tapeworm infections such as cysticercosis, and infections by trematodes (flukes).

What is the mechanism of action?

Praziquantel increases permeability of the cell membrane to calcium, which causes tetanic contraction of the trematode muscle and death of the trematode.

What is the route of administration?

Oral. Praziquantel is rapidly absorbed after administration and distributes readily to the CNS.

How is it metabolized?

Praziquantel is metabolized in the liver and excreted through the urine.

What are the adverse effects?

Drowsiness, dizziness, nausea, headache

NICLOSAMIDE (Niclocide)

What is this drug's therapeutic use?

Niclosamide is the drug of choice for most cestode (tapeworm) infections. The drug is ineffective against cysticercosis (use praziquantel) and *Echinococcus granulosus* (use mebendazole). "Nicholas plays with tape."



What is the mechanism of action?

Niclosamide inhibits mitochondrial anaerobic phosphorylation of adenosine diphosphate within cestodes.

What is this drug's toxicity?

Toxic effects of niclosamide are mild and may include GI disturbance, headache, and fever.

49

Antiviral Drugs

Define virus.

A virus is an obligate intracellular parasite; its metabolic processes, such as synthesis of proteins and DNA, depend on the host cell.

Can all viruses be pharmacologically treated?

No. Most drugs cannot distinguish between host cell functions and viral functions. Therefore, the drugs would cause significant toxicity to both.

List the steps in viral replication.

1. Absorption and penetration of host cells
 2. Synthesis of early nonstructural proteins, such as nucleic acid polymerases
 3. Synthesis of RNA and DNA
 4. Synthesis of late structural proteins
 5. Assembly of virus particles
- Antiviral drugs usually inhibit one of these steps (Figure 49-1).

What is the easiest way to remember the antiviral drugs?

By classifying them according to which virus they attack

DRUGS USED TO TREAT HERPESVIRUS INFECTION

Name five drugs used to treat herpesvirus infection.

1. Foscarnet
 2. Ganciclovir
 3. Idoxuridine
 4. Vidarabine
 5. Acyclovir
- “For herpes, GIV acyclovir.”



What pathogens are included in the herpesvirus family?

Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2)
Varicella-zoster virus
Cytomegalovirus (CMV)
Epstein-Barr virus

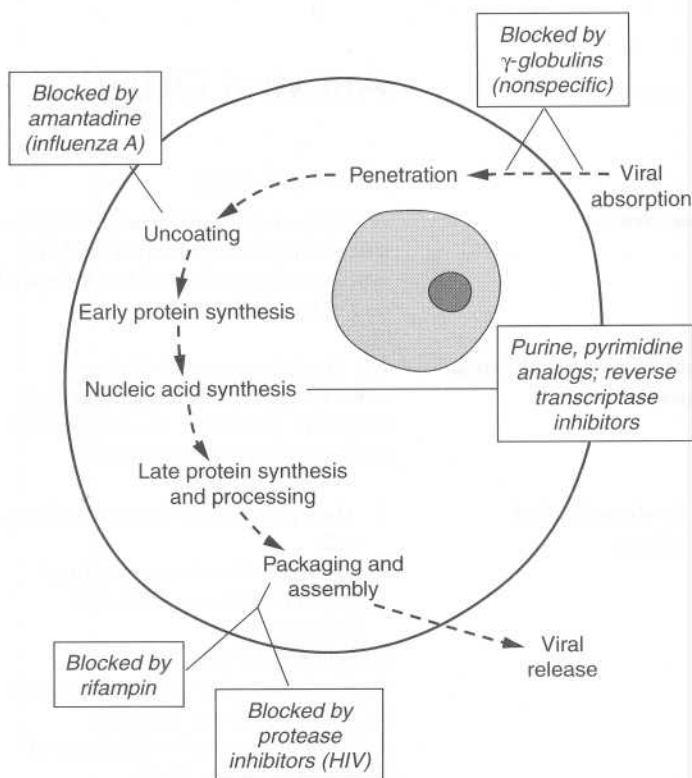


Figure 49-1. Sites of action of some antiviral drugs.

ACYCLOVIR (Zovirax)

What is it?

Acyclovir is a guanine analog.

What is its mechanism of action?

Acyclovir is monophosphorylated by a herpes enzyme called thymidine kinase. Later it is di- and triphosphorylated by the host cell. The active triphosphate form of acyclovir is then incorporated into viral DNA, which causes premature DNA-chain termination (Figure 49-2).

For what would you prescribe acyclovir?

HSV-1, which causes diseases of the mouth, face, skin, esophagus, and brain

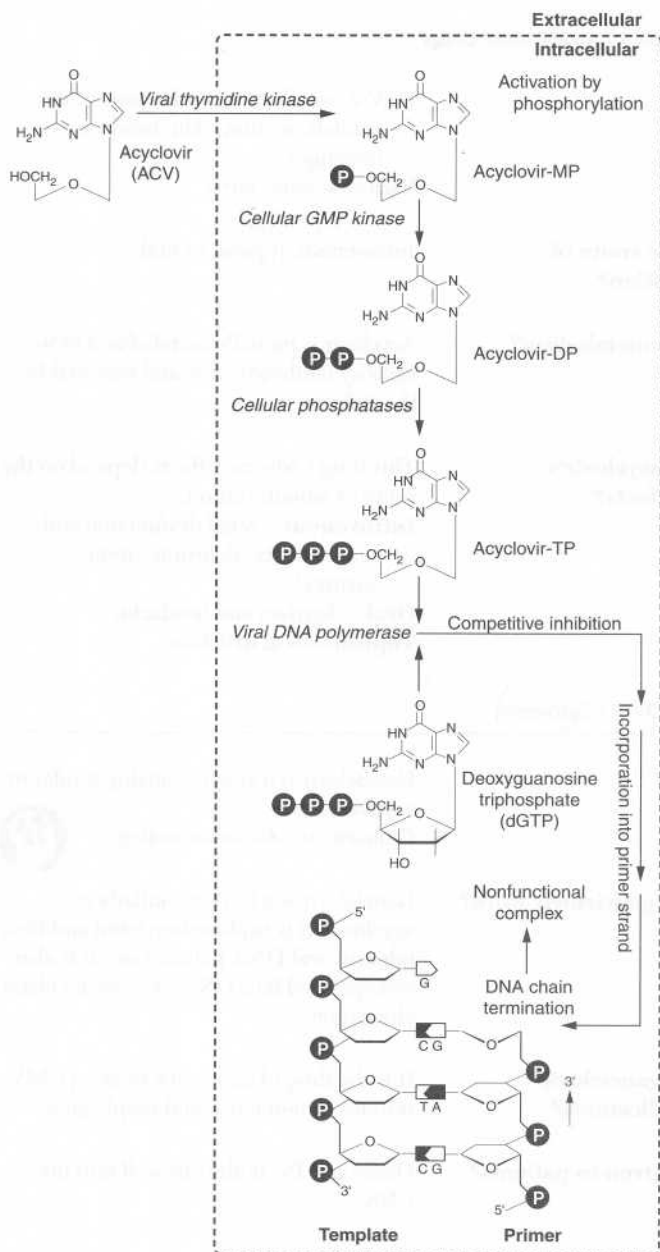


Figure 49-2. Conversion of acyclovir to acyclovir triphosphate, leading to DNA chain termination. Uninfected cells convert very little or no drug to the phosphorylated derivatives. Thus, acyclovir is selectively activated in cells infected with herpesviruses that code for appropriate thymidine kinases. Incorporation of acyclovir-MP from acyclovir-TP into the primer strand during viral DNA replication leads to chain termination and formation of an inactive complex with the viral DNA polymerase. (Redrawn from Hardman JG, Limbird LE [eds]: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th ed. New York, McGraw-Hill, 1996, p 1195. Used with permission of The McGraw-Hill Companies.)

HSV-2, which causes infections of the genitals, rectum, skin, hands, or meninges
Varicella-zoster virus

What is the route of administration?

Intravenous, topical, or oral

What is its metabolism?

Acyclovir is partially metabolized to 9-carboxy methylguanide and excreted by the kidneys.

What are acyclovir's adverse effects?

This drug's adverse effects depend on the route of administration:

Intravenous—renal dysfunction and neurotoxicity (delirium, tremor, seizures)

Oral—diarrhea and headache

Topical—local irritation

GANCICLOVIR (Cytovene)

What is it?

Ganciclovir is a guanine analog similar to acyclovir.

Ganciclovir—Guanine analog



How does ganciclovir work?

Ganciclovir works very similarly to acyclovir. It is triphosphorylated and then inhibits viral DNA polymerase. It is also incorporated into DNA, decreasing chain elongation.

What are ganciclovir's clinical indications?

It is the drug of choice for treating CMV, retinitis, pneumonia, and esophagitis.

How is it given to patients?

Orally and IV. It absorbs well into the CNS.

How is ganciclovir metabolized?

By renal excretion

What are ganciclovir's adverse effects?

Bone marrow suppression

Renal dysfunction

Seizures

Fever

GI disturbances

IDOXURIDINE (Stoxil) AND TRIFLURIDINE (Viroptic)

What is idoxuridine?	A thymidine analog.
What is its mechanism of action?	Idoxuridine is converted into an active triphosphate form by cellular enzymes and is incorporated into DNA, making it more susceptible to breakage.
What are idoxuridine's clinical uses?	Treatment of herpes simplex keratitis and vaccinia virus keratitis
What is its route of administration?	Idoxuridine is administered only by ophthalmic solution or ointment.
What is trifluridine?	A newer ophthalmic drug similar to idoxuridine but even more effective against herpes simplex keratitis
What are the adverse effects of idoxuridine?	Conjunctival irritation and photophobia

VIDARABINE (Vira-A)

What is it?	Vidarabine is an adenosine analog.
What is its mechanism of action?	Like acyclovir, vidarabine is converted into an active triphosphate form within the host cell and then inhibits viral DNA synthesis.
What is its clinical use?	Vidarabine is used to treat HSV-1 encephalitis and keratitis. It is also used against varicella zoster in immunocompromised patients. It is not effective against HSV-2.
What is the route of administration?	Vidarabine is given parentally or topically (ophthalmic).
What is its metabolism?	Vidarabine is excreted by the kidneys.
Describe vidarabine's adverse effects.	Gastrointestinal (GI) effects— <i>anorexia, nausea</i> CNS effects— <i>paresthesias, tremor</i> Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) Hypokalemia Hepatic dysfunction

FOSCARNET (Foscavir)

What type of drug is it?	Foscarnet is not a nucleoside analog; it is a phosphonate analog that does not rely on phosphorylation for activation.
What is foscarnet's mechanism of action?	It inhibits replication by blocking the pyrophosphate binding site of viral DNA polymerase.
How is foscarnet administered?	Only by the intravenous route
What is its clinical use?	Foscarnet is used in the treatment of CMV infections (retinitis).
How is foscarnet metabolized?	It is excreted through the kidneys.
What are foscarnet's adverse effects?	Nephrotoxicity Electrolyte abnormalities such as hypocalcemia and hypomagnesemia Seizures

OTHER AGENTS

Name three other newer agents used to treat herpesvirus.	1. Sorivudine 2. Trifluridine 3. Fanciclovir
What is their mechanism of action?	These drugs also work by inhibiting viral DNA synthesis. (They are not discussed in detail here because they have not yet been tested on the USMLE Step 1.)

DRUGS USED TO TREAT RESPIRATORY VIRUSES

Which drugs are used in the treatment of respiratory viruses?	Amantadine, rimantadine, and ribavirin
--	--

AMANTADINE AND RIMANTADINE

What are amantadine and rimantadine?	Amantadine and its derivative rimantadine are uniquely configured tricyclic amines.
What is their mechanism of action?	Amantadine and rimantadine inhibit viral uncoating.

What is viral uncoating?	Viruses enter cells through endosomes, which are membrane-bound vacuoles that surround the virus particle. Acidification of the endosome is needed for the virus to uncoat and transfer its genetic material to the cytoplasm.
What is the action of these drugs on the viral endosome?	Amantadine and rimantadine act as weak bases to prevent acidification of the endosome.
What is their therapeutic use?	Amantadine and rimantadine are used mainly for influenza A prophylaxis in elderly and immunosuppressed populations.
What is the route of administration?	Amantadine and rimantadine are well absorbed orally.
What is their metabolism?	They are excreted by the kidneys.
What are their adverse effects?	Insomnia, dizziness, and ataxia. These symptoms are less common with rimantadine because it does not cross the blood-brain barrier.

RIBAVIRIN

Describe this drug.	Ribavirin is a synthetic guanosine analog.
What is ribavirin's mechanism of action?	The mechanism of action is not completely clear, but it is thought to decrease synthesis of guanosine triphosphate, inhibit 5' capping of viral mRNA, and interfere with viral RNA-dependent RNA polymerase of certain viruses.
What is ribavirin's major therapeutic use?	Treatment of infants and young children who are suffering from respiratory syncytial virus bronchiolitis and pneumonia
What other clinical uses does this drug have?	Ribavirin is also used occasionally for treating influenza A and B and Lassa fever.
How is this drug administered?	Ribavirin is effective when administered orally, intravenously, and by aerosol methods.

What is ribavirin's toxicity? Dose-dependent transient hemolytic anemia and elevated bilirubin levels

Should this drug be used in pregnant women? No! It is teratogenic.

INTERFERONS

What are they? Interferons are a family of naturally existing glycoproteins or cytokines that possess antiviral actions.

What are the therapeutic uses for interferons? Condyloma acuminatum
Chronic hepatitis B and C
Kaposi's sarcoma
Hairy cell leukemia

What are the adverse effects of interferons? An acute flulike syndrome including headache, fever, chills, and muscle aches is the most common adverse effect. However, interferons may also cause neurotoxicity, cardiotoxicity, thyroid dysfunction, and bone marrow depression.

DRUGS USED TO TREAT HIV INFECTION AND AIDS

Define acquired immunodeficiency syndrome (AIDS). AIDS, caused by the human immunodeficiency virus (HIV), is characterized by a CD4 count of less than 200 and the presence of opportunistic infections.

How is the CD4 count calculated? White blood cells (WBCs) \times % lymphocytes \times % CD4 cells

How does HIV differ from other viruses? HIV is a retrovirus. After entering the host cell, it undergoes reverse transcription and is then incorporated into the host cell's DNA.

List two surrogate markers that help to predict the risk of progression from HIV positive to AIDS. The CD4 count and HIV RNA PCR (polymerase chain reaction), which is commonly called the *viral load*

What are some uses of the viral load test? It can predict progression to AIDS, and it is also used for therapeutic monitoring.

Which two viral enzymes do anti-retroviral medications inhibit?	<ol style="list-style-type: none"> 1. Reverse transcriptase 2. Protease
What is the action of reverse transcriptase?	It converts viral RNA into DNA.
What is the action of viral protease?	It cleaves viral protein into infectious virions.
What are the two types of reverse transcriptase inhibitors (RTIs)?	<ol style="list-style-type: none"> 1. Nucleoside analogs 2. Non-nucleoside analogs
Give four examples of nucleoside analog RTIs.	<ol style="list-style-type: none"> 1. Zidovudine (AZT) 2. Didanosine (ddI) 3. Zalcitabine (ddC) 4. Stavudine (d4T)
What is zidovudine?	A structural analog of thymidine
Describe didanosine.	It is a structural analog of adenosine.
What is zalcitabine?	A structural analog of cytosine
Describe stavudine.	It is a structural analog of thymidine.
What is the mechanism of action of these drugs?	They are phosphorylated and incorporated into viral DNA by reverse transcriptase. They then terminate chain elongation once they are incorporated into the viral DNA.
What are the side effects of AZT?	Anemia Neutropenia Headache Fatigue Myalgia
What are the side effects of ddI?	Acute pancreatitis, painful peripheral neuropathy, nausea, and vomiting
What are the side effects of ddC?	Peripheral neuropathy, GI effects, and arthralgia
What are the side effects of zalcitabine and stavudine?	Painful sensory peripheral neuropathy

Give some examples of non-nucleoside analog reverse transcriptase inhibitors (NNRTIs).

Nevirapine (Viramune) and delavirdine (Rescriptor)

Give some examples of protease inhibitors.

Saquinavir (Invirase)
Ritonavir (Norvir)
Indinavir (Crixivan)
Nelfinavir (Viracept)

What are the side effects of saquinavir?

Diarrhea, abdominal discomfort, and nausea

What are the side effects of ritonavir?

Nausea, abdominal pain, vomiting, circumoral paresthesias, abnormal elevations in liver function tests, and increased cholesterol levels

What are the side effects of indinavir?

Nausea, vomiting, increased bilirubin levels, abdominal pain, and nephrolithiasis

What are the side effects of nelfinavir?

Diarrhea and flatulence

DRUGS USED TO PREVENT INFECTION IN PATIENTS WITH HIV

Which vaccines *should* be given to patients who have HIV?

Pneumococcal, hepatitis, and influenza vaccines

Which vaccines *should not* be given to patients with HIV?

Live vaccines such as the oral polio vaccine and varicella vaccine

Medications are used for primary prophylaxis of which infections?

Pneumocystis carinii pneumonia (PCP)
Mycobacterium avium-complex (MAC)
Mycobacterial tuberculosis (TB)

What are the indications for PCP prophylaxis?

Prior PCP infection
CD4 count of less than 200 cells per cubic millimeter
HIV-associated thrush
Unexplained fevers over 100°F for more than 2 weeks

Which medications are used for PCP prophylaxis?

Bactrim, dapsone, and aerosolized pentamidine

What are the indications for MAC prophylaxis?	CD4 count less than 50 and prior diagnosis of MAC
Which medications are used for MAC prophylaxis?	Clarithromycin, azithromycin, and rifabutin
What are the indications for TB prophylaxis?	Tuberculin skin test (TST) ≥ 5 mm Prior positive TST results without treatment Contact with active case of TB
Which medications are used for TB prophylaxis?	Isoniazid and rifampin
What are the side effects of isoniazid?	Hepatitis, rash, and peripheral neuropathy
What are the side effects of rifampin?	Hepatitis and GI upset

DRUG THERAPY FOR OPPORTUNISTIC INFECTIONS IN PATIENTS WITH HIV

What medications are used to treat PCP?	Bactrim Pentamidine Atovaquone
What medications are used to treat <i>Toxoplasma</i> infection?	A combination of pyrimethamine and sulfadiazine A combination of pyrimethamine and clindamycin
What medications are used to treat esophageal <i>Candida albicans</i>?	Fluconazole, ketoconazole, and amphotericin B
What medications are used to treat MAC?	Macrolides (clarithromycin or azithromycin), plus one of the following: Ethambutol Ciprofloxacin Amikacin
What medications are used to treat <i>Cryptococcus</i> infection?	Amphotericin, fluconazole, and itraconazole
What medications are used to treat <i>Cytomegalovirus</i>?	Ganciclovir and foscarnet

HIV POST-EXPOSURE PROPHYLACTIC MEDICATIONS

Which body fluids have been documented to carry HIV?	Blood, semen, vaginal secretions, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid
Which body fluids have <i>not</i> been documented to carry HIV?	Feces, nasal secretions, sputum, saliva, sweat, tears, urine, and vomitus
Which medication has established efficacy when used for post-exposure prophylaxis?	AZT
Which medications should be prescribed for the recipient of a deeply penetrating hollow-bore needle stick injury from a host who has HIV?	<ol style="list-style-type: none"> 1. AZT 2. Lamivudine (a new nucleoside analog RTI) 3. Indinavir
How soon after exposure should these medications be started?	As soon as possible-preferably within 1 to 2 hours

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Drugs Used to Treat Tuberculosis and Leprosy

What is the No. 1 cause of death from infectious disease worldwide?

Tuberculosis (TB)

TUBERCULOSIS

Which organism causes tuberculosis?

Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis*.

What makes tuberculosis difficult to treat?

There are three major complicating factors:

1. *Mycobacterium tuberculosis* is an intracellular organism.
2. The organism grows very slowly. Consequently infections are often chronic, and therapy may be required for as long as 2 years.
3. Resistance to drugs develops rapidly.

Why is tuberculosis treated with multiple drugs?

Multiple drugs are used to delay the emergence of resistant strains of the organism.

What are the five first-line pharmacologic treatment options for tuberculosis?

1. Isoniazid (INH)
2. Rifampin
3. Pyrazinamide
4. Ethambutol
5. Streptomycin

ISONIAZID (Laniazid)

How does this drug work?

Isoniazid is believed to act by inhibiting the synthesis of mycolic acids which are unique to the mycobacterial cell walls.

What is the route of administration?

The drug is readily absorbed orally and parenterally. Absorption is impaired, however, if isoniazid is taken with aluminum-containing antacids.

What is this drug's distribution?

Isoniazid penetrates all body fluids, cells, and caseous material. Therefore, it is able to act on intracellular mycobacteria.

State the metabolism of the drug.

Isoniazid is metabolized in the liver by *N*-acetylation. The rate of acetylation shows a genetic variance among humans; it can be as fast as 1 hour or as slow as 3 hours.

How does isoniazid affect the cytochrome P-450 system?

Isoniazid inhibits this system; the drug therefore increases plasma levels of drugs such as phenytoin, benzodiazepines, and warfarin.

State isoniazid's adverse effects.

Peripheral neuritis—This thought to be caused by isoniazid binding and inactivating pyridoxine (vitamin B₆). Vitamin B₆ supplementation can prevent this problem.
Hepatotoxicity—Jaundice and hepatitis can be severe.
Rashes and skin eruptions
Neurologic problems such as convulsions in patients prone to seizures

When is isoniazid given alone?

In most cases isoniazid is given along with other drugs. However, for prophylactic treatment of skin test converters and for close contacts of patients who have active disease, isoniazid is given alone.

Can you use isoniazid in pregnant patients?

No! This drug crosses the placenta and may cause peripheral neuritis in newborns.

RIFAMPIN (Rifadin)

What is its mechanism of action?

Rifampin inhibits the β -subunit of DNA-dependent RNA polymerase. It suppresses RNA synthesis by blocking chain initiation.

What is the metabolism of this drug?

Rifampin is metabolized by and induces the cytochrome P-450 system. Therefore, other drugs such as ketoconazole and warfarin may require higher dosages to maintain therapeutic concentrations.

State the clinical indications for rifampin in addition to the treatment of tuberculosis.

Prophylaxis of meningitis in meningococcemia caused by *Haemophilus influenzae* and *Neisseria meningitidis*
Leprosy—used in combination with dapsone
Legionnaires' disease—used in combination with erythromycin

What is the absorption and distribution of the drug?

Rifampin is orally absorbed. It easily penetrates into all tissue cells and fluids, including the CNS.

State the adverse effects.

Urine, sweat, tears, and other secretions may become red-orange in color.

(Rifampin—Red-orange)

Rash, fever, nausea, and vomiting are common.



A flulike syndrome with chills, fever, and myalgias may develop in patients who use rifampin once or twice weekly.

PYRAZINAMIDE (Pyrazinamide)

When is this drug used?

For short-course treatment of tuberculosis in combination with isoniazid and rifampin

What are the absorption and distribution of this drug?

It is orally absorbed and distributed to most body tissues, including the CNS.

State the mechanism of action.

Unknown

What are pyrazinamide's adverse effects?

Hepatotoxicity
Gout due to the inhibition of uric acid secretion
Arthralgia and myalgia (common)

ETHAMBUTOL (Myambutol)

What is the clinical use of this drug?

Ethambutol is almost always used against *M. tuberculosis*, but it can be used against *M. kansasii* as well.

How does it work?	The mechanism of action is not completely known, but it is thought to inhibit arabinogalactan an essential component of mycobacterial cell wall.
State the absorption and distribution of the drug.	It is well absorbed orally and distributes into all cells, including the CNS.
Is this drug bacteriostatic or bacteriocidal?	Ethambutol is the only first-line drug that is bacteriostatic.
What are the adverse effects?	Optic neuritis or other visual disturbances (decreased visual acuity, red-green color blindness) Gout due to a decrease in uric acid secretion

STREPTOMYCIN

See Chapter 43—*Protein Synthesis Inhibitors* for more detailed information on streptomycin.

What is the classification of this drug?	Streptomycin is an aminoglycoside.
What is its mechanism of action?	Streptomycin binds to the 30S ribosomal subunit, causing a misinterpretation of the genetic code.
State the clinical indication for streptomycin.	Treatment of life-threatening tuberculosis in combination with other first-line drugs
What are streptomycin's adverse effects?	Ototoxicity Nephrotoxicity—usually reversible

TREATMENT GUIDELINES

What is the current recommendation for the initial treatment of active TB?	A 2-month regimen of pyrazinamide, INH, and rifampin, and a 4-month regimen of INH and rifampin, for a total of 6 months
Name three second-line agents used in the treatment of tuberculosis.	1. Ethionamide 2. Aminosalicyclic acid (PAS) 3. Cycloserine

Why are these drugs second-line agents?	They are lower in efficacy and higher in toxicity.
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DRUGS USED TO TREAT LEPROSY

What organism causes leprosy?	<i>Mycobacterium leprae</i>
What are the pharmacologic treatment options for leprosy?	Dapsone clofazimine and rifampin

DAPSONE

How does dapsone work?	It is related to the sulfonamides and inhibits folate biosynthesis by acting as a competitive antagonist of PABA.
What is this drug's route of administration?	Oral
What is the metabolism of this drug?	It undergoes acetylation in the liver.
How is it used?	Dapsone is used in combination with rifampin and clofazimine to treat leprosy.
What are the adverse reactions?	GI irritation Methemoglobinemia Hemolysis (<i>dose-related</i>) especially in patients with G6PD deficiency Drug-induced lupus erythematosus

CLOFAZIMINE (Lamprene)

How does this drug work?	Clofazimine binds to DNA and inhibits DNA template function.
When is clofazimine used?	This drug is given to patients who are unable to tolerate dapsone.
What are the adverse effects?	A distinctive reddish-brown discoloration of the skin GI irritation (nausea, vomiting, diarrhea)

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Section XI

Toxicology

Toxicology

What is toxicology?

The study of the adverse effects of chemicals and physical agents on biological systems

Name the six steps in managing a poisoned patient.

1. Stabilize the patient (use the ABCs of first aid).
2. Identify the toxin (by toxicology screen).
3. Prevent toxin absorption (by gastric lavage, activated charcoal, and other such techniques).
4. Institute specific antidotal therapy.
5. Enhance toxin elimination (by changing urine pH, hemodialysis).
6. Monitor the patient.

TOXICITIES AND TREATMENTS OF COMMONLY USED DRUGS AND CHEMICALS

Acetaminophen

What are the signs and symptoms of acetaminophen toxicity?

Nausea, vomiting, anorexia, and diaphoresis. Acetaminophen toxicity is often asymptomatic until 24 to 48 hours after ingestion, when hepatotoxicity becomes evident.

What is the Rumack-Matthew nomogram?

A graph used to indicate possible hepatotoxicity and the need for antidotal therapy based on a patient's serum acetaminophen level

How long after ingestion should a serum acetaminophen level be drawn for correlation on the nomogram?

Between 4 to 24 hours after ingestion

How is acetaminophen toxicity treated?

1. Gastric lavage within 2 hours
2. Activated charcoal administration
3. Administration of *N*-acetylcysteine if indicated by the Rumack-Matthew nomogram

How is N-acetylcysteine administered?

Loading dose of 140 mg/kg orally
Maintenance dose of 70 mg/kg orally
every 4 hours for 17 doses

β -Adrenergic Blockers

Name the signs and symptoms of β -adrenergic blocker toxicity.

Nausea
Vomiting
Hypotension
Bradycardia
CNS depression

How do you treat β -adrenergic blocker toxicity?

1. Perform gastric lavage.
2. Administer glucagon 5–10 mg IV, then 1–5 mg IV per hour.
3. Administer atropine or cardiac pacing if hemodynamically significant bradycardia exists.
4. Give IV fluids and vasopressors for treatment of hypotension.

Benzodiazepines

What are the signs and symptoms of benzodiazepine toxicity?

Weakness, ataxia, and (in severe cases) coma and respiratory depression.
Benzodiazepine overdose rarely causes death.

How do you treat benzodiazepine toxicity?

1. Perform gastric lavage.
2. Administer activated charcoal.
3. Administer flumazenil, a competitive benzodiazepine receptor antagonist.

How is flumazenil administered?

In incremental doses of 0.2, 0.3, and 0.5 mg IV at 1-minute intervals until the desired effect is achieved or a maximum dose of 3 to 5 mg has been given

Why shouldn't flumazenil be administered in cases of benzodiazepine overdose associated with poly-pharmacy overdose?

Because it may cause seizures in patients who have co-ingested stimulants. Flumazenil may also cause seizures in patients who have a history of chronic benzodiazepine use.

Calcium Channel Blockers

What are the signs and symptoms of calcium channel blocker toxicity?

Bradycardia
Hypotension
CNS depression
Constipation

How do you treat calcium channel blocker toxicity?

1. Perform gastric lavage.
2. Administer calcium chloride 10% IV at 0.2 ml/kg over 5 minutes.
3. Administer atropine, glucagon, or cardiac pacing for hemodynamically significant bradycardia.
4. Use amrinone, vasopressors, or an intra-aortic balloon pump in refractory cases of hypotension.

Cyanide

How does cyanide affect human cells?

It inhibits cytochrome oxidase and therefore blocks electron transport, which results in decreased aerobic energy production.

What are the signs and symptoms of cyanide toxicity?

Nausea
Vomiting
Tachycardia
Hypertension
Arrhythmias
Apnea
Acute respiratory distress syndrome
Coma

What odor can sometimes be detected on the breath of a person who has cyanide poisoning?

A bitter almond odor

How is cyanide toxicity treated?

1. Gastric lavage
2. Lilly cyanide antidote kit—amyl nitrite pearls for inhalation, 3% sodium nitrite IV, and 25% sodium thiosulfate IV
3. High-dose oxygen therapy

How does the nitrite therapy work?

Nitrites induce methemoglobinemia. Methemoglobin has a higher affinity for cyanide than does cytochrome oxidase; therefore, the cyanide dissociates from the cytochrome oxidase more efficiently.

Ethylene Glycol

Where is ethylene glycol commonly found?

In antifreeze and windshield de-icers.

What are the signs and symptoms of ethylene glycol toxicity?

Nausea
 Vomiting
 Abdominal pain
 Ataxia
 Seizures
 Coma

How do you treat ethylene glycol toxicity?

1. Give ethanol 5% to 10% in 5% dextrose in water (D5W) IV, or 20% to 30% solution orally. Maintain blood alcohol level > 100 mg/dl.
 2. Use hemodialysis in severe cases of renal failure.
 3. Give pyridoxine (vitamin B₆), 50 mg IV every 6 hours.
 4. Give thiamine 100 mg IM every 6 hours.
 5. Give folic acid 1 mg orally every day.
- Activated charcoal is *not* effective in adsorbing ethylene glycol.

Isoniazid**What are the signs and symptoms of isoniazid toxicity?**

Nausea
 Vomiting
 Dizziness
 Slurred speech
 Lethargy
 Hepatic injury
 Seizures
 Coma

How is isoniazid toxicity treated?

1. Gastric lavage
2. Activated charcoal administration
3. Pyridoxine (5 g IV) and diazepam to control seizures
4. Hemodialysis in severe cases

Isopropyl Alcohol**Where is isopropyl alcohol commonly found?**

In antifreeze and rubbing alcohol

What are the signs and symptoms of isopropyl alcohol toxicity?

Nausea
 Vomiting
 Abdominal pain
 Ataxia
 Respiratory depression

How is isopropyl alcohol toxicity treated?

1. Gastric lavage
2. Supportive therapy—IV fluids and bicarbonate administration to correct acidosis
3. Hemodialysis in severe cases with renal failure

Activated charcoal is *not* effective in adsorbing isopropyl alcohol.

Lithium

What are the signs and symptoms of lithium toxicity?

Lethargy
Dysarthria
Delirium
Seizures
Coma

How is lithium toxicity treated?

1. Gastric lavage and entire bowel irrigation
2. Administration of IV fluids
3. Administration of sodium polystyrene sulfonate
4. Hemodialysis in severe cases

Activated charcoal is *not* effective in adsorbing lithium.

Methanol

Where is methanol commonly found?

In antifreeze, solvents, and bootleg (homemade) alcohol ("moonshine")

What are the signs and symptoms of methanol toxicity?

Nausea
Vomiting
Abdominal pain
Blurred vision
Blindness
Seizures
Coma

How is methanol toxicity treated?

1. Use ethanol 5% to 10% in D5W IV, or 20% to 30% solution orally. Maintain blood alcohol level > 100 mg/dl.
 2. Use hemodialysis in severe cases of renal failure.
 3. Administer thiamine and folate.
- Activated charcoal is *not* effective in adsorbing methanol.

Opioids

What are the signs and symptoms of opioid toxicity?

Miosis
Altered mental status
Bradycardia
Respiratory depression
Hypothermia

How is opioid toxicity treated?

With naloxone 2 mg IV, which is short acting and therefore may require a continuous infusion

Salicylates

What are the early- and late-stage acid-base disorders associated with salicylate toxicity?

Early stage—respiratory alkalosis secondary to tachypnea
Late stage—metabolic acidosis

What are the signs and symptoms of salicylate toxicity?

Nausea
Vomiting
Tinnitus
Hyperthermia
Coagulopathy
Hypoglycemia
Acute renal failure
Coma

How can the severity of a patient's toxicity be determined?

A serum level can be collected. A peak level < 3 mmol/L is associated with no symptoms; a level of 3 to 7 mmol/L is associated with mild-to-moderate symptoms; and a level > 7 mmol/L is associated with severe toxicity.

What is the treatment for salicylate toxicity?

1. Gastric lavage
2. Activated charcoal
3. Saline diuresis and alkalization of the urine to a pH of 8 to increase urinary excretion of salicylates
4. Hemodialysis in severe cases

Theophylline

What are the signs and symptoms of theophylline toxicity?

Nausea
Vomiting
Irritability
Tachypnea
Tachycardia
Hypotension
Arrhythmias

At what serum level do seizures and cardiac arrhythmias typically occur?

At 40 to 60 mg/L (normal = 10–20 mg/L)

How is theophylline toxicity treated?

1. Gastric lavage
2. Activated charcoal
3. Hemodialysis in severe cases—acute ingestion with serum level > 80 mg/L, or chronic ingestion with serum level > 60 mg/L
4. β -adrenergic blockers to reverse tachycardia and hypotension.

Tricyclic Antidepressants

Name the signs and symptoms of tricyclic antidepressant toxicity.

Mild overdose—predominance of anticholinergic side effects, such as mydriasis, hallucinations, urinary retention, hypertension, and tachycardia

Severe overdose—CNS depression along with seizures, hypotension, and cardiotoxicity.

QRS complex > 0.10 seconds on the ECG correlates with an increased risk of seizures and cardiac arrhythmias.

How can one determine the severity of a patient's overdose?

Serum levels can be used for diagnosis as well as determining severity:

—Serum level < 1000 nmol/L = therapeutic

—Serum level > 3300 nmol/L = severe overdose

Name the steps for treating tricyclic antidepressant toxicity.

1. Gastric lavage
 2. Activated charcoal
 3. Supportive therapy—airway protection (intubation), ECG monitoring, and IV fluids
 4. Norepinephrine, phenylephrine, or dopamine for hypotension
 5. Phenytoin or diazepam for seizures
- Use of ipecac syrup to induce emesis is contraindicated in treating tricyclic antidepressant toxicity.

CHELATORS AND HEAVY METALS

What is a chelator (chelating agent)?

A chelator is a molecule with two or more electronegative groups that is used to

bind toxic metals in stable complexes. These complexes have relatively low toxicity and enhanced fecal and renal excretion. Chelators are used in the treatment of heavy metal toxicities.

Name the five most commonly used chelators.

1. Ethylenediamine tetra-acetic acid (EDTA)
2. Dimercaprol (also known as BAL)
3. Penicillamine
4. Deferoxamine
5. Succimer

EDTA

What is the primary use of EDTA?

Treating lead poisoning

How is it administered?

Parenterally (IV or IM)

What is the most important adverse effect of EDTA?

Nephrotoxicity (reversible)

Why must the calcium disodium salt of EDTA be used?

Because the sodium salt of EDTA can cause severe hypocalcemia

Dimercaprol

For what reason was dimercaprol first developed?

As an antidote for lewisite, an arsenical war gas. It was first named BAL (British anti-lewisite).

What is dimercaprol used to treat?

Mercury, arsenic, lead, and cadmium toxicities

How must it be administered?

Parenterally (IM)

What are the contraindications to dimercaprol administration?

Concurrent use of iron therapy (iron forms a toxic complex with dimercaprol)
Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency
Allergy to peanut oil (dimercaprol is administered intramuscularly in a solution of peanut oil)

Penicillamine

What is it used to treat?

Poisoning by copper (Wilson's disease), lead, arsenic, mercury, and gold as well as rheumatoid arthritis and cystinuria

How is penicillamine administered? Enterally. (Penicillamine is the only commercially available oral chelating agent for adults.)

What adverse effects can result from administration of this chelating agent? Rash
Fever
Leukopenia
Thrombocytopenia resembling a penicillin hypersensitivity reaction
Rare side effects include the following:
Aplastic anemia
Stevens-Johnson syndrome
Lupus erythematosus

Deferoxamine

What is this chelator used to treat? Acute iron (ferrous salts) intoxication

How is deferoxamine administered? Parenterally

Does it compete for heme iron in hemoglobin and cytochromes? Yes, but very poorly

What adverse effects are associated with deferoxamine administration? Neurotoxicity
Hepatic and renal dysfunction
Severe coagulopathies
Histamine release and hypotensive shock when given by rapid IV infusion

Succimer

Succimer is an oral congener of which of the other chelating agents? Dimercaprol

What is the only FDA-approved use of this chelating agent? Treatment of childhood lead intoxication with serum levels $> 45 \mu\text{g/dl}$

Name the adverse effects associated with succimer administration. Transient increase in hepatic transaminase levels
Skin rash
GI distress

HEAVY METALS

Arsenic

Where is arsenic commonly found?

Organic arsenic—ubiquitous in the environment

Inorganic arsenic—insecticides, fungicides, rodenticides, and compounds used in glass manufacturing

Arsine gas—produced in smelting of metals and making of silicon microchips and lead plating

How does arsenic cause toxicity?

It interferes with oxidative phosphorylation.

What are the signs and symptoms of acute arsenic toxicity?

GI distress—nausea, vomiting, rice-water stools

Cardiovascular effects—hypotension and arrhythmias

CNS effects—seizure and coma

Hematologic effects—hemolysis and bone marrow depression

Renal effects—acute tubular necrosis and oliguria

List the signs and symptoms of chronic arsenic toxicity.

Polyneuritis

Skin changes—erythroderma, hyperkeratosis, Aldrich-Mees lines (transverse white striae of the fingernails)

What is the characteristic smell of the breath of a patient who is experiencing acute arsenic toxicity?

A sweet, garlicky odor

How can arsenic intoxication be detected?

Through serum arsenic levels

What is the treatment for acute arsenic toxicity?

1. Gastric lavage
2. Dimercaprol or penicillamine
3. Hemodialysis if the patient has renal failure

Lead

Where is lead commonly found?

It is ubiquitous in nature. Lead salts may be found in paints made before 1978.

How is lead absorbed?	Through ingestion or inhalation
Are the toxic effects of chronic lead exposure different between children and adults?	In some respects, yes: Childhood form —abdominal pain, anemia, and subclinical CNS effects, such as mental retardation and learning disabilities Adult form —abdominal pain, anemia, peripheral neuropathy, ataxia, memory loss, and renal disease
Which is more common, acute or chronic lead toxicity?	Chronic lead toxicity
How can lead intoxication be detected?	Through serum lead levels
What is the treatment for lead toxicity.	<ol style="list-style-type: none"> 1. Remove the source of lead exposure. 2. Perform gastric lavage if the lead was ingested. 3. Administer EDTA, dimercaprol, penicillamine, or succimer. (Deferoxamine is the <i>only</i> chelator that <i>cannot</i> be used to treat lead toxicity.)

Mercury

Where is mercury commonly found?	In batteries, thermometers, and dental fillings
Has a correlation between dental fillings and mercury intoxication been scientifically proved?	No
Through what route does mercury intoxication commonly occur?	Through inhalation. However, this metal may be ingested or absorbed through the skin.
What are the signs and symptoms of acute mercury intoxication?	GI distress—nausea and vomiting Chest pain and shortness of breath secondary to inflammation of airways and interstitial pneumonitis CNS effects—intention tremor, increased excitability, and delirium

List the signs and symptoms of chronic mercury intoxication.

CNS effects as with acute toxicity
Loosening of the teeth, gingivitis, and stomatitis
Excessive salivation

How is mercury toxicity detected?

Through serum mercury levels

What is the treatment for mercury toxicity?

1. Removal of the source of mercury exposure
2. Gastric lavage, if the mercury was ingested
3. Dimercaprol, penicillamine, or succimer

AIR POLLUTANTS

List the major air pollutants in industrialized countries and briefly describe them.

Carbon monoxide (50%)—colorless, odorless
Sulfur oxides—colorless
Nitrogen oxides—brownish gas
Ozone
Hydrocarbons—colorless

Carbon Monoxide (CO)

What commonly produces CO?

Combustion of fossil fuels and cigarette smoking

How does carbon monoxide adversely affect the human body?

CO causes tissue hypoxia because the affinity of CO for hemoglobin is more than 200-fold greater than that of oxygen.

What are some symptoms of CO toxicity?

Headache
Confusion
Loss of visual acuity
Syncope (occurs when approximately 40% of hemoglobin has been converted to carboxyhemoglobin)
Coma

How do you treat carbon monoxide exposure?

1. Remove the patient from the CO source.
2. Have the patient breathe 100% oxygen. *Hyperbaric oxygen* accelerates the clearance of CO.

Sulfur Dioxide (SO₂)

What commonly produces sulfur dioxide?

Combustion of fossil fuels
Manufacturing of sulfuric acid
Refrigerants

How does SO₂ adversely affect the human body?

It forms sulfurous acid on contact with moist mucous membranes.

What signs and symptoms result from SO₂ exposure?

Conjunctival and bronchial irritation
Epistaxis
Delayed pulmonary edema (severe exposure)

How do you treat sulfur dioxide exposure?

1. Remove the patient from the source of exposure.
2. Relieve irritation and inflammation with supportive therapies.

Nitrogen Dioxide (NO₂)

What occupations involve increased risk of NO₂ exposure?

Farming and firefighting would both increase the risk of exposure. NO₂ is formed in silage on farms and is also a by-product of fires.

How does nitrogen dioxide adversely affect the human body?

It causes deep lung irritation and pulmonary edema, and may also cause irritation of the eyes, nose, and throat.

How do you treat NO₂ exposure?

There is no specific treatment, but measures should be taken to reduce the risk of exposure.

Ozone (O₃)

What commonly produces O₃?

Ozone is produced in water and air purification devices as well as arc welding.

How does O₃ adversely affect the human body?

Acute exposure—irritation and dryness of mucous membranes

Chronic exposure—can lead to emphysema, bronchitis, bronchiolitis, and pulmonary fibrosis

How do you treat O₃ exposure?

There is no specific treatment, but symptomatic therapies to decrease inflammation and pulmonary edema should be attempted. Also, the patient should be removed from the source of exposure.

Hydrocarbons

What commonly produces hydrocarbons?	Industrial and cleaning solvents
Name some common examples of everyday hydrocarbons.	Benzene Toluene Carbon tetrachloride
How do hydrocarbons adversely affect the human body?	They are potent CNS depressants, and thus can cause nausea, vertigo, headache, and coma.
What ill effects can benzene cause?	Bone marrow suppression with pancytopenia
How do you treat hydrocarbon exposure?	Remove the patient from the source of exposure and provide supportive therapies.

INSECTICIDES

What are the three major classes of insecticides?	<ol style="list-style-type: none"> 1. Chlorinated hydrocarbons—DDT 2. Organophosphorus insecticides 3. Botanical agents—nicotine, rotenone, pyrethrum
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Chlorinated Hydrocarbons

How do chlorinated hydrocarbons adversely affect the human body?	They block physiologic inactivation of nerve membranes in the sodium channels, thus causing uncontrollable firing of action potentials.
How do you treat chlorinated hydrocarbon exposure?	There is no specific treatment, but measures should be taken to remove the person from the exposure.
Are the chlorinated hydrocarbons still available as insecticides?	No. They were removed from the market because of their long half-lives (years) and their severe environmental toxicity.

Organophosphates

How do organophosphates function?	They irreversibly inhibit acetylcholinesterase and increase the levels of acetylcholine at the muscarinic and nicotinic synapses.
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What are the signs and symptoms of organophosphate toxicity?

Nicotinic effects—fasciculations, weakness, hypertension, and tachycardia

Muscarinic effects—nausea, vomiting, abdominal cramps, urinary and fecal incontinence, sweating, salivation, and miosis. If the toxicity is severe, bradycardia, respiratory failure, and hypotension may also occur.

How is organophosphate toxicity treated?

Initial treatment depends on the mode of exposure:

If absorbed through the skin—All contaminated clothes should be removed, and the skin should be washed thoroughly.

If inhaled—The patient should be removed from the site of exposure.

If ingested—Gastric lavage, followed by activated charcoal treatment, should be initiated.

After initial treatment:

Atropine (0.5 to 2 mg IV every 15 to 20 minutes until desired effect) can be used for treating muscarinic side effects.

Pralidoxime (1 to 2 grams IV over 5 to 20 minutes every 4 to 6 hours until desired effect) can be used for treating nicotinic side effects.

Airway management and supportive therapy are initiated.

Botanical Insecticides

Name three botanical insecticides.

1. Nicotine
2. Rotenone
3. Pyrethrum

How does nicotine function as an insecticide?

Nicotine causes excitation of nicotinic receptors, followed by paralysis of ganglionic, CNS, and neuromuscular transmission.

How is nicotine toxicity treated?

Treatment is supportive with special attention paid to avoiding convulsions.

What adverse effects are caused by rotenone?	GI irritation, conjunctivitis, and dermatitis
How is rotenone toxicity treated?	Treatment is symptomatic.
What symptoms occur if high doses of pyrethrum are inhaled or absorbed?	Contact dermatitis, excitation, and convulsions
How is pyrethrum toxicity treated?	Treatment is symptomatic.

HERBICIDES

What are the two major agents used as herbicides?	1. Paraquat 2. Chlorophenoxyacetic acid
By what route of exposure does paraquat cause toxicity to the human body?	Ingestion
What are the manifestations of paraquat toxicity?	GI irritation with bloody stools and vomiting Pulmonary impairment that usually leads to pulmonary fibrosis and death, which typically occurs within 1 to 2 days of exposure
Is there an antidote for paraquat exposure?	No
What is the mortality rate after ingestion of 5 ml or more of paraquat?	Greater than 50%
How do you treat paraquat exposure?	With gastric lavage, supportive therapies, and hemodialysis
What are the major signs of chlorophenoxyacetic acid toxicity?	Coma, muscle hypotonia, and dermatitis
How is the toxicity treated?	Treatment consists of gastric lavage and supportive therapy.

SPECIFIC ANTIDOTES

What are the specific antidotes for the following drugs?

Opioids	Naloxone
Carbon monoxide	100% oxygen
β-adrenergic blockers	Glucagon
Benzodiazepines	Flumazenil
Theophylline	Esmolol
Isoniazid	Pyridoxine
Ethylene glycol and methanol	Ethanol
Digoxin	Digoxin-specific antibodies
Acetylcholinesterase inhibitors (organophosphates)	Atropine and pralidoxime
Acetaminophen	N-acetylcysteine
Calcium channel blockers	Calcium chloride and glucagon
Cyanide	Nitrites and thiosulfate
Iron	Deferoxamine
Mercury, arsenic, and gold	Dimercaprol
Coumadin	Vitamin K and fresh frozen plasma
Heparin	Protamine sulfate
Nitrites	Methylene blue

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Pharmacology Power Review

Pharmacology Power Review

52

Pharmacology Power Review

The Pharmacology Power Review follows this general format:

drug name

Mechanism of action. **Rx:** Therapeutic uses. **Tox:** Side effects. **Other:** Additional important or unique properties of a drug such as contraindications, metabolism, or drug interactions. Included only for some drugs.

Only high-yield drugs and facts are discussed in the Pharmacology Power Review. For further details, refer to the chapters in parentheses.

CHOLINERGIC AGONISTS (Chapter 6)

Direct-Acting Agonists

acetylcholine

An endogenous cholinomimetic that acts on both muscarinic and nicotinic receptors. **Rx:** Occasionally used intraocularly for miosis in cataract surgery. In general it is used infrequently because it is rapidly hydrolyzed, but synthetic derivatives of acetylcholine such as bethanechol are used. **Tox:** Excessive cholinergic stimulation—remember *dumbels*: **d**iarrhea, **u**rination, **m**iosis, **b**ronchoconstriction, **e**xcitation (of CNS and skeletal muscle), **i**lacrimation, and **s**alivation.



bethanechol

A carbamic acid ester with little nicotinic activity but strong muscarinic activity that increases smooth muscle contractions of bowel and bladder. **Rx:** Bowel or bladder atony. **Tox:** dumbels.



carbachol

A carbamic acid ester that stimulates both muscarinic and nicotinic receptors. **Rx:** Open-angle glaucoma. **Tox:** dumbels.



pirelcarpine

Primarily a muscarinic agonist. **Rx:** Glaucoma. **Tox:** CNS disturbances (headache, visual difficulties) along with excessive cholinergic stimulation (dumbels).



methacholine

A choline ester that stimulates primarily muscarinic receptors. **Rx:** Used to test for asthma and bronchial hyperreactivity. **Tox:** Generalized cholinergic stimulation.

Indirect-Acting Agonists

isofluorophate, echothiophate, parathion

Organophosphates *irreversibly* bind to and inhibit acetylcholinesterase, the enzyme responsible for metabolizing acetylcholine. **Rx:** Parathion is used as an insecticide. Isofluorophate and echothiophate are used occasionally for glaucoma and accommodative esotropia. **Tox:** Excessive cholinergic stimulation (dumbels).



physostigmine

A reversible cholinesterase inhibitor that **can enter the CNS**. **Rx:** Glaucoma, accommodative esotropia, bowel and bladder atony; overdoses of atropine, phenothiazines, and tricyclic antidepressants. **Tox:** Convulsions, muscle paralysis, excessive cholinergic stimulation.

neostigmine

A reversible cholinesterase inhibitor that does not enter the CNS. **Rx:** Treatment of myasthenia gravis, paralytic ileus, urinary retention; antidote for nondepolarizing neuromuscular blockade such as with tubocurarine. **Tox:** Excessive cholinergic stimulation (dumbels).



edrophonium

A reversible cholinesterase inhibitor. **Rx:** Diagnosis of myasthenia. **Tox:** Excessive cholinergic stimulation.

pyridostigmine

A reversible cholinesterase inhibitor similar to edrophonium but with a longer half life. **Rx:** Therapy of myasthenia gravis. **Tox:** Excessive cholinergic stimulation (dumbels).

**CHOLINERGIC ANTAGONISTS (Chapter 7)****atropine, homatropine**

These drugs are primarily, muscarinic blockers. **Rx:** Atropine is used to treat bradycardia and serves as an antidote for organophosphate poisoning. Both agents are used in ophthalmology as cycloplegics and mydriatics. **Tox:** Decreased secretion, decreased vision, delusions, hyperthermia, dilation of cutaneous vessels. "Dry as a bone, blind as a bat, mad as a hatter, hot as a hare, and red as a beet."

**scopolamine**

Nonselective cholinergic blocker. **Rx:** Similar to atropine but particularly beneficial in the treatment of motion sickness. **Tox:** Similar to atropine.

Neuromuscular Blockers**tubocurarine, pancuronium**

Nondepolarizing neuromuscular agents that competitively inhibit acetylcholine at nicotinic receptors. **Rx:** Used as adjuvant drugs in anesthesia; with these agents, less anesthetic is required to produce muscle relaxation. Tubocurarine is used by hunters to cause muscle paralysis in prey. **Tox:** Ganglionic blockade, histamine release; may result in hypotension and bronchospasm.

succinylcholine

A **depolarizing** neuromuscular blocking agent that reversibly binds acetylcholine receptors. **Rx:** Skeletal muscle relaxation for surgical procedures. **Tox:** Hypotension, arrhythmias; can cause respiratory collapse, malignant hyperthermia.

Ganglionic Blockers**hexamethonium, trimethaphan, nicotine**

Ganglionic inhibitors block the nicotinic receptors of both the parasympathetic

and sympathetic ganglia. **Rx:** Used in the past for hypertensive emergencies. **Tox:** Nonselective parasympathetic and sympathetic blockade.

ADRENERGIC AGONISTS (Chapter 8)

α Agonists

phenylephrine

An α_1 agonist that activates the PIP_2 cascade. **Rx:** Nasal decongestant, mydriatic (no cycloplegia), and hypotension. **Tox:** Rebound mucosal swelling, hypertensive headache.

methoxamine

Similar to phenylephrine; binds α_1 receptors and activates the PIP_2 cascade. **Rx:** Hypotension, paroxysmal atrial tachycardia; also used as a mydriatic. **Tox:** Elevated blood pressure may lead to pulmonary edema, cerebral hemorrhage, or cardiac necrosis.

clonidine

Stimulates presynaptic α_2 receptors on sympathetic neurons. **Rx:** Hypertension, withdrawal from benzodiazepines and opiates. **Tox:** Orthostatic hypotension, dry mouth, sexual dysfunction.

β Agonists

Dobutamine

A synthetic analog of dopamine that stimulates primarily β_1 receptors but has some activity at α_1 and β_2 receptors. **Rx:** Short-term management of acute CHF. **Tox:** Arrhythmias, headache, hypertension, palpitations.

isoproterenol

Stimulates β_1 and β_2 receptors. **Rx:** Treatment of bradycardia or heart block. **Tox:** Tachycardia, headache, flushing of skin, anginal pain.

albuterol, metaproterenol, terbutaline

Stimulate both types of β receptors but preferentially β_2 over β_1 . **Rx:** Treatment of asthma and COPD, suppression of premature labor (terbutaline). **Tox:** Tremor, restlessness, tachycardia. **Other:** Systemic side effects are minimal since these drugs are usually inhaled.

α and β Agonists***norepinephrine***

Acts on α_1 , α_2 , and β_1 receptors; vasoconstricts, increases BP and CO, and causes reflex bradycardia due to vagal responses. **Rx:** Severe hypotension, as in shock. **Tox:** Arrhythmias, respiratory distress, headache.

epinephrine

Acts on all α and β receptors. **Rx:** Anaphylaxis, bronchospasm; used as a nasal decongestant and ophthalmic vasoconstrictor, and as an adjuvant with local anesthetics. **Tox:** Hypertension, cardiac arrhythmias, headache. **Other:** Contraindicated in patients who are on nonselective β blockers because the unopposed α response may lead to severe hypertension.

dopamine

A neurotransmitter and agonist at dopamine, α_1 , β_1 , and β_2 receptors. **Rx:** Used to increase renal blood flow and to increase blood pressure in cases of shock. **Tox:** Arrhythmias, respiratory distress.

Indirect Agonists***amphetamine***

Releases stored norepinephrine and dopamine from the presynaptic nerve terminal. **Rx:** Used to treat ADHD and narcolepsy, and as an appetite suppressant. **Tox:** Confusion, insomnia, headache, restlessness, palpitation.

ephedrine

Stimulates release of norepinephrine from nerve terminals but can directly stimulate adrenergic receptors as well. **Rx:** Treatment of enuresis, hypotension. **Tox:** Arrhythmias, insomnia.

ADRENERGIC ANTAGONISTS (Chapter 9) **α Blockers*****prazosin, terazosin, doxazosin***

α_1 -selective blockers decrease peripheral vascular resistance and relax smooth muscle in the prostate. **Rx:** Treatment of hypertension, benign prostatic hypertrophy. **Tox:** First-dose

hypotension, syncope, sexual dysfunction, lethargy, dry mouth.

phentolamine

A reversible nonselective α blocker. **Rx:** Short-term management of pheochromocytoma-induced hypertension. **Tox:** Orthostatic hypotension, reflex tachycardia, impotence.

phenoxybenzamine

An **irreversible** α_1 and α_2 blocker. **Rx:** Treatment of pheochromocytoma-induced hypertension, carcinoid syndrome, Raynaud's phenomenon. **Tox:** Orthostatic hypotension.

β Blockers

propranolol

Nonselective β blocker prototype. **Rx:** Myocardial infarction, migraine, hypertension, and tachycardia; also used as an antianginal and antiarrhythmic, and to treat thyrotoxicosis. **Tox:** Bradycardia, heart block, fatigue, impotence; may mask signs of hypoglycemia in diabetics. **Other:** Contraindicated in asthmatics because it induces bronchoconstriction.

timolol

A nonselective competitive β antagonist given only as an ophthalmic solution. **Rx:** Glaucoma. **Tox:** Similar to propranolol but milder because there is less systemic absorption.

pindolol

A nonselective β antagonist with intrinsic sympathomimetic activity, which means that it acts as a partial agonist at β receptors. **Rx:** Hypertension in patients with a propensity for bradycardia. **Tox:** Similar to propranolol.

**metoprolol, atenolol,
esmolol, acebutolol**

β_1 selective blockers. **Rx:** Treatment of hypertension, angina, and arrhythmias. Atenolol is similar to metoprolol but longer acting. Esmolol is similar to metoprolol but very short acting; it is often given IV in surgical situations. **Tox:** Similar to propranolol but less bronchoconstriction.

labetalol

β blocker that also has α_1 selective blockade. **Rx:** Hypertension, atrial fibrillation. **Tox:** Hypotension, fatigue.

Postganglionic Adrenergic Neuronal Blockers

guanethidine

Enters peripheral nerves via the reuptake mechanism for norepinephrine and blocks the release of norepinephrine from storage vesicles. **Rx:** Treatment of hypertension in the past. **Tox:** Orthostatic hypotension, sexual dysfunction.

reserpine

A *Rauwolfia* alkaloid that blocks a nerve terminal's ability to store norepinephrine by blocking its transport from cytoplasm into intracellular storage vesicles. **Rx:** Hypertension (very rarely used). **Tox:** Sedation mental depression, bradycardia.

ANXIOLYTICS, HYPNOTICS, AND SEDATIVES (Chapter 11)

Benzodiazepines

diazepam, triazolam, temazepam, alprazolam, flurazepam

Benzodiazepines stimulate the binding of GABA to the GABA_A receptor, which results in hyperpolarization of the cell membrane and decreased neuronal excitability. **Rx:** Anxiety, seizures, insomnia, alcohol withdrawal. **Tox:** Drowsiness, ataxia, dizziness. **Other:** Individual benzodiazepines differ mainly in half-life.

Benzodiazepine Antagonists

flumazenil

Competitive antagonist of benzodiazepines at the GABA_A receptor. **Rx:** Reversal of benzodiazepine sedation or overdose. **Tox:** Few in benzo-free individuals.

Azaspirones

buspirone

A partial agonist at serotonin (5HT_{1A}) receptors. **Rx:** Relieves anxiety with minimal sedation. **Tox:** Headache, nausea, dizziness.

Carbamates

meprobamate

Mechanism of action is unknown but it does act as a CNS depressant. **Rx:** Anxiolytic. **Tox:** Respiratory depression, ataxia.

Barbiturates

phenobarbital, pentobarbital, thiopental

Barbiturates increases GABA neuronal transmission, which subsequently increases Cl^- channel activity and decreases neuronal excitability. **Rx:** Treatment of seizures and agitation, and as an adjuvant in anesthesia. **Tox:** Psychological and physical dependence, CNS depression, cough, and bronchospasm.

ANTIPSYCHOTICS (CHAPTER 12)

Phenothiazines

chlorpromazine, promethazine, thioridazine, fluphenazine, trifluoperazine

These agents block dopamine D_2 receptors in the mesolimbic and mesocortical paths. **Rx:** Used to treat schizophrenia, intractable hiccups (chlorpromazine), and as antiemetic and antipruritic agents. **Tox:** Sedation, hypotension, anticholinergic effects.

Thioxanthenes

thiothixene

Blocks dopamine D_2 receptors. **Rx:** Treatment of schizophrenia. **Tox:** Extrapyramidal effects, tardive dyskinesia, hypotension, anticholinergic effects.

Butyrophenones

haloperidol, droperidol

These agents are high-potency dopamine D_2 receptor blockers in the CNS. **Rx:** Schizophrenia and other psychotic disorders, agitation; used as antipruritics. **Tox:** Extrapyramidal effects (parkinsonism, dystonia, akathisia), tardive dyskinesia, weight gain, infertility, anticholinergic effects.

Atypical Agents

clozapine

Blocks dopamine D₁ and D₂ receptors.

Rx: Schizophrenia. **Tox:** Agranulocytosis, convulsions, hypotension, sedation.

Other: Atypical agents have a lower likelihood of causing extrapyramidal symptoms.

risperidone

Antagonist at serotonin 5-HT₂ receptors.

Rx: Schizophrenia. **Tox:** Hypotension.

PHARMACOTHERAPEUTICS OF DEPRESSION AND MANIA (Chapter 13)

Tricyclics

imipramine, amitriptyline, amoxapine, desipramine, doxepin, trimipramine, nortriptyline, clomipramine

These agents inhibit the reuptake of norepinephrine and serotonin.

Imipramine and amitriptyline are prototypes. **Rx:** Clinically significant depression, phobias, and obsessive-compulsive disorder. **Tox:** Postural hypotension, sedation, anticholinergic effects (dry mouth, urinary retention, tachycardia), arrhythmias. **Other:** Imipramine is used to treat enuresis in children.

SSRI Inhibitors

fluoxetine, sertraline, paroxetine, fluvoxamine, trazodone

These agents preferentially inhibit reuptake of serotonin over norepinephrine and dopamine. **Rx:** Often first-line agents for clinical depression. Fluoxetine is also used for obsessive-compulsive disorder. **Tox:** Usually well tolerated. May cause sedation, postural hypotension, tachycardia.

MAO Inhibitors

isocarboxazid, tranylcypromine, phenelzine

These drugs block MAO-A, which is responsible for the metabolism of serotonin, norepinephrine, and tyrosine. **Rx:** Second-line agents for depression. **Tox:** Overdose can lead to hyperthermia, hepatotoxicity, impotence, and hypertensive crisis if consumed with large amounts of tyrosine.

Atypical Antidepressants

bupropion

Mechanism of action not well understood. **Rx:** Treatment of depression. **Tox:** Headache, nausea, tachycardia, restlessness.

Drugs Used to Treat Mania

lithium

Unclear mechanism of action; believed to block the enzyme inositol-1-phosphatase. **Rx:** Treatment of bipolar disease, SIADH. **Tox:** Tremor, vomiting, abdominal cramps, nephrogenic diabetes insipidus, ataxia, seizures, thyroid enlargement. **Other:** Contraindicated in pregnancy. Thiazides increase lithium concentration.

ANTI-EPILEPTIC DRUGS (Chapter 14)

phenytoin

Binds to and prolongs the inactivated states of Na^+ channels; increases GABA-mediated inhibitory postsynaptic potentials. **Rx:** Treatment of tonic-clonic and partial seizures, status epilepticus after administration of diazepam, digitalis-induced arrhythmias. **Tox:** Gingival hyperplasia, nystagmus, diplopia, ataxia, fetal hydantoin syndrome (characterized by abnormal growth and development). **Other:** Contraindicated in sinus bradycardia or AV block. Significantly increases the cytochrome P_{450} system.

valproic acid

Like phenytoin, it appears to prolong the inactivated states of Na^+ channels; it also may increase GABA concentrations. **Rx:** Treatment of absence, myoclonic, and partial seizures. **Tox:** Nausea, vomiting, sedation, hepatotoxicity, neural tube defects. **Other:** Contraindicated in pregnancy.

phenobarbital

Long-acting barbiturate that potentiates synaptic inhibition through an action on the GABA receptor. **Rx:** Treatment of febrile seizures in children, and partial and tonic-clonic seizures. **Tox:** Respiratory, cardiac, and mental sedation,

	nystagmus, psychotic reactions, hypersensitivity reactions.
primidone	Works similarly to phenytoin by blocking Na^+ channels from repolarizing. Rx: An alternative choice for adults with partial seizures (both simple and complex) and generalized tonic-clonic seizures. Tox: Sedation, ataxia, nausea, vomiting, drowsiness. Rarely, Stevens-Johnson syndrome.
carbamazepine	Potentiates synaptic inhibition by blocking Na^+ channels. Rx: Drug of choice for partial and tonic-clonic seizures and for trigeminal neuralgia. Tox: Severe liver toxicity—patients need frequent liver function tests while on the drug; aplastic anemia; agranulocytosis.
ethosuximide	Inhibits Ca^{2+} influx through low-threshold T-type channels in thalamic neurons. Rx: Drug of choice for absence seizures. Tox: GI disturbances.
diazepam, clonazepam	Benzodiazepines potentiate GABA transmission. Rx: Diazepam—status epilepticus. Clonazepam—absence and myoclonic seizures. Tox: Drowsiness, sedation.

DRUGS USED TO TREAT PARKINSON'S DISEASE AND OTHER MOVEMENT DISORDERS (Chapter 15)

levodopa/carbidopa	Levodopa crosses the blood-brain barrier and is converted to dopamine. Carbidopa increases CNS concentration of levodopa; it inhibits conversion of levodopa to dopamine in the periphery by blocking dopa decarboxylase. Rx: Parkinson's disease. Tox: Confusion, delusion, hallucination, dyskinesias, anorexia, nausea, tachycardia, postural hypotension.
selegiline	Selectively inhibits MAO-B and therefore increases dopamine concentration. Rx: Parkinson's disease. Tox: Dyskinesia, mood alterations.

amantadine

This antiviral agent works by both increasing release and delaying reuptake of dopamine in the nigra striatum. **Rx:** Parkinson's disease. **Tox:** Restlessness; a bluish discoloration of the legs known as livedo reticularis.

bromocriptine

An ergot alkaloid that acts as a strong **agonist** at presynaptic D₂ receptors. **Rx:** Treatment of Parkinson's disease, acromegaly, and conditions involving hyperprolactinemia such as amenorrhea, galactorrhea, and infertility. **Tox:** Hypotension, gastrointestinal distress, and mental confusion and delusions.

benztropine

A tertiary amine alkaloid that blocks cholinergic output of neurons in the corpus striatum. **Rx:** Parkinson's disease. **Tox:** Anticholinergic effects.

ANESTHETIC DRUGS (Chapter 16)

Inhaled Agents

halothane, isoflurane, enflurane

The mechanism of action of these agents is unclear, but they are thought to increase the threshold for activating CNS neurons. **Rx:** Anesthesia. **Tox:** Malignant hyperthermia, hepatotoxicity.

Intravenous Agents

thiopental, thiamylal

Ultra-short-acting barbiturates that, like other barbiturates, enhance GABA transmission. **Rx:** Induction of anesthesia. **Tox:** Bronchospasm, cough. **Other:** Contraindicated in acute intermittent porphyria because this condition predisposes to widespread demyelination of the CNS and PNS.

diazepam, midazolam, lorazepam

These benzodiazepines potentiate GABA transmission. **Rx:** Can be used as the sole anesthetic agents for procedures that do not require analgesia (e.g., cardiac catheterization, endoscopy, cardioversion), or in combination with other agents to induce anesthesia. **Tox:** Severe drowsiness.

propofol

Unclear mechanism of action. **Rx:** Induction and maintenance of anesthesia, and sedation during intensive care. **Tox:** Apnea, severe hypotension.

morphine, fentanyl

Opioid analgesics. See *Chapter 18—Opioid Analgesics and Antagonists* for discussion of mechanisms of action. **Rx:** Used in combination with inhaled agents to produce general anesthesia. **Tox:** Severe respiratory and cardiac depression.

ketamine

Structurally similar to phencyclidine (PCP); known as a dissociative anesthetic that blocks N-methyl d-aspartate (NMDA) receptors. **Rx:** Emergency surgical procedures, trauma. **Tox:** Hallucinations.

Local Agents

lidocaine, tetracaine, procaine, bupivacaine, benzocaine

These compounds are weak bases that block nerve transmission by inhibiting Na^+ channels. **Rx:** Surface anesthesia, nerve block, epidural anesthesia. **Tox:** Paraesthesias, allergic reactions, bradycardia.

CNS STIMULANTS (Chapter 17)

Methylxanthines

caffeine, theophylline, theobromine

These agents increase cGMP and cAMP by inhibiting phosphodiesterase and blocking adenosine receptors. **Rx:** Theophylline is used in asthma treatment. **Tox:** Insomnia, agitation, tremor, convulsions, arrhythmias.

Amphetamines

methylphenidate, methamphetamine, dextroamphetamine

Amphetamines release neuronal stores of catecholamines, especially norepinephrine and dopamine. **Rx:** Used to decrease fatigue and insomnia; also used for appetite control and in ADHD. **Tox:** Irritability, anorexia, nausea, palpitations, angina.

ALCOHOL AND OTHER DRUGS OF ABUSE (Chapter 18)

Ethanol

Ethanol is a CNS depressant that works through GABA receptors to enhance GABA-mediated synaptic transmission.

Rx: Treatment of methanol overdose, ethylene glycol overdose. **Tox:** Euphoria, disinhibition, slurred speech, decreased liver function (hepatitis and cirrhosis may develop), gastrointestinal irritation, inflammation, gynecomastia, testicular atrophy.

PCP

Phencyclidine, also known as “angel dust,” is a dissociative anesthetic (loss of pain without loss of consciousness) that blocks NMDA (N-methyl D-aspartate) receptors. **Rx:** None. **Tox:** Schizophrenia-like psychosis, increased blood pressure and heart rate, limb numbness, ataxia, hypersalivation, and seizures that may be fatal.

marijuana

Also known as “weed,” or “hash”; the active component is α -9THC (tetrahydrocannabinol), which acts upon its own specific receptors. **Rx:** Treatment of nausea in patients undergoing chemotherapy. **Tox:** Increased heart rate and blood pressure, injected conjunctiva, dry mouth, bronchodilation, and hunger.

LSD

Lysergic acid diethylamide interacts with serotonin 5-HT receptors in the mid-brain. **Rx:** None. **Tox:** Mydriasis, tachycardia, flushing, increased blood pressure.

cocaine

Blocks reuptake of norepinephrine by inhibiting presynaptic α_2 receptors. **Rx:** Can be used for surface anesthesia. **Tox:** Fatal coronary vasospasm or arrhythmias; seizures.

OPIOID ANALGESICS AND ANTAGONISTS (Chapter 19)

Full Agonists

morphine, hydromorphone

Binds primarily to μ receptors. **Rx:** Used for severe, constant pain; sometimes used in acute pulmonary edema. **Tox:**

	Respiratory depression, constipation, histamine release, psychological and physiological dependence.
meperidine	Binds to μ receptors. Rx: Treatment of acute pancreatitis, because it does not induce gastrointestinal spasms. Tox: Similar to morphine.
fentanyl	Similar to morphine (binds to μ receptors) but 80x more potent. Rx: Used as an anesthetic. Tox: Same as morphine.
heroin	An illicit narcotic. Rx: None. Tox: Coma, respiratory depression, pinpoint pupils.
codeine	Binds to μ and δ receptors; to receptors; approximately 10 \times less potent than morphine. Rx: Antitussive, mild analgesia. Tox: Similar to morphine.
methadone	Works similarly to morphine (binds to μ receptors) but has a longer duration of action. Rx: Treatment of opioid withdrawal syndromes. Tox: Similar to morphine.

Partial Agonists

buprenorphine, pentazocine	Agonist at κ and σ receptors, and antagonist at μ receptors. Rx: Analgesia—relief of moderate to severe pain. Tox: Psychotomimetic effects, respiratory depression.
nalbuphine	Agonist at κ receptors, antagonist at μ receptors. Rx: Relief of moderate to severe pain. Tox: Similar to morphine.

Opioid Antagonists

naloxone	Competitive antagonist at μ receptors. Rx: Reverses the effects of acute opiate overdose (pupil constriction, respiratory depression, constipation). Tox: Transient tachypnea.
naltrexone	Competitive antagonist at μ receptors. Rx: For opiate overdose. Tox: Same as

naloxone. **Other:** Unlike naloxone, naltrexone can be given orally and is longer acting; therefore, it is better for outpatient management of opiate abuse.

ANTIHYPERTENSIVE DRUGS (Chapter 20)

Centrally Acting Drugs

methyldopa, clonidine

Cause peripheral vasodilation and reduction in cardiac output through stimulation of central α_2 receptors. **Rx:** Treatment of moderate to severe hypertension. **Tox:** Drowsiness, headache, decreased libido, hepatotoxicity. Clonidine is associated with rebound hypertension after sudden withdrawal.

α Blockers

prazosin, terazosin, doxazosin

α_1 -selective blockers that decrease peripheral vascular resistance and relax smooth muscle in the prostate. **Rx:** Treatment of hypertension. **Tox:** First-dose hypotension, syncope, sexual dysfunction, lethargy, benign prostatic hypertrophy, dry mouth.

β Blockers

propranolol

Nonselective β blocker prototype. **Rx:** Used to treat hypertension and tachycardia; as an antianginal and antiarrhythmic; for MI prophylaxis; and to treat thyrotoxicosis. **Tox:** Bradycardia, heart block, fatigue, impotence; may mask signs of hypoglycemia in patients with diabetes. **Other:** Contraindicated in asthmatics because it induces bronchoconstriction.

metoprolol, atenolol, esmolol, acebutolol

β_1 -selective blockers. **Rx:** Treatment of hypertension, angina, and arrhythmias. Atenolol is similar to metoprolol but longer acting. Esmolol is similar to metoprolol but very short acting; it is often given IV in surgical situations. **Tox:** Similar to propranolol but less bronchoconstriction.

labetalol

β blocker that also has α_1 selective blockade. **Rx:** Hypertension, atrial fibrillation. **Tox:** Hypotension, fatigue.

Ganglionic Blockers***trimethaphan, hexamethonium***

Ganglionic inhibitors block the nicotinic receptors of both the parasympathetic and sympathetic ganglia. **Rx:** Used in the past for hypertensive emergencies. **Tox:** Nonselective parasympathetic and sympathetic blockade.

Postganglionic Adrenergic Neuronal Blockers***guanethidine***

Enters peripheral nerves via the reuptake mechanism for norepinephrine and blocks the release of norepinephrine from storage vesicles. **Rx:** Used in the past for treatment of hypertension. **Tox:** Orthostatic hypotension, sexual dysfunction.

reserpine

A *Rauwolfia* alkaloid that blocks a nerve terminal's ability to store norepinephrine by blocking its transport from cytoplasm into intracellular storage vesicles. **Rx:** Hypertension (very rarely used). **Tox:** mental depression, bradycardia.

Direct Vasodilators***hydralazine***

Increases cGMP which leads to dephosphorylation of myosin and relaxation of arteriolar smooth muscle. **Rx:** Treatment of moderate hypertension, CHF. **Tox:** Lupus-like syndrome (👉 board question), hypotension, reflex tachycardia, palpitations, angina, nausea, diarrhea.

minoxidil

A potent arterial vasodilator that works by opening K^+ channels, which results in hyperpolarization and relaxation of smooth muscle cells. **Rx:** Treatment of severe hypertension. **Tox:** Edema due to sodium and water retention, reflex tachycardia, flushing, pericardial lesions.

sodium nitroprusside

Increases intracellular cGMP, which subsequently leads to diminished

intracellular Ca^{2+} ions, causing vasodilation of both arteries and veins. **Rx:** Used in hypertensive emergencies. **Tox:** Hypotension, arrhythmias, cyanide toxicity.

diazoxide

Opens K^+ channels, causing hyperpolarization and relaxation of arterial smooth muscle cells. **Rx:** Used in hypertensive emergencies. **Tox:** Hypotension, edema, hyperglycemia secondary to inhibition of insulin release, tachycardia.

Calcium Channel Blockers

verapamil, diltiazem, nifedipine

These agents bind to and inhibit L-type Ca^{2+} channels. **Rx:** Treatment of hypertension, angina, arrhythmias. **Tox:** Headache, heart block, dizziness, CHF, peripheral edema, flushing. **Other:** Verapamil has the greatest negative inotropic effect; nifedipine has the least.

Diuretics

hydrochlorothiazide, furosemide, ethacrynic acid, bumetanide

See listing in this Power Review under **DIURETICS (Chapter 23)**.

ACE Inhibitors

captopril, lisinopril, enalapril

These agents block the conversion of angiotensin I to angiotensin II. **Rx:** Treatment of mild to moderate hypertension, CHF. **Tox:** Cough, hyperkalemia, and dizziness; proteinuria and renal failure in patients with bilateral renal artery stenosis.

losartan, valsartan

Angiotensin II receptor antagonists. **Rx:** Hypertension. **Tox:** Hypotension, hyperkalemia, headache.

ANTIARRHYTHMIC DRUGS (Chapter 21)

Class IA

quinidine

Binds to open Na^+ channels, preventing Na^+ influx and thus decreasing the slopes of phase 0 and phase 4. **Rx:** Treatment of

ventricular and supraventricular arrhythmias. **Tox:** Diarrhea, nausea, vomiting, cinchonism (fever, vertigo, tinnitus), increased QT interval, increased digoxin levels, widening of the QRS duration.

disopyramide

Mechanism of action similar to quinidine.

Rx: Ventricular arrhythmias. **Tox:** Significant negative inotrope properties and antimuscarinic properties (dry mouth, blurred vision, constipation)

procainamide

Mechanism of action similar to that of quinidine. **Rx:** Second-line agent for treatment of ventricular arrhythmias.

Tox: Lupus-like effect (⚠ board question), increased QT interval.

Class IB

lidocaine

Blocks Na^+ channels and shortens phase 0 of the action potential. **Rx:** Treatment of ventricular arrhythmias, especially post-MI. **Tox:** Drowsiness, slurred speech, paraesthesias, agitation.

phenytoin

Works similarly to lidocaine. **Rx:** Treatment of digitalis-induced arrhythmias. **Tox:** Gingival hyperplasia, nystagmus, diplopia, ataxia, fetal hydantoin syndrome (characterized by abnormal growth and development).

tocainide

Works similarly to lidocaine. **Rx:** Treatment of ventricular arrhythmias. **Tox:** Pulmonary fibrosis.

mexiletine

Works similarly to lidocaine. **Rx:** Treatment of ventricular arrhythmias. **Tox:** Tremor, blurred vision, lethargy.

Class IC

flecainide, propafenone, moricizine

Class IC drugs block Na^+ channels and suppress phase 0 upstroke. **Rx:** Treatment of refractory ventricular arrhythmias. **Tox:** Pro-arrhythmogenic dizziness, nausea. **Other:** Propafenone displays some β blockade activity.

Class II (β Blockers)*propranolol, metoprolol, sotalol, esmolol*

These agents diminish phase 4 depolarization and thus decrease automaticity, prolong AV conduction, and decrease heart rate. **Rx:** Treatment of tachyarrhythmias. **Tox:** Bradycardia, heart block, fatigue, impotence; may mask signs of hypoglycemia in diabetics. **Other:** Propranolol is contraindicated in asthmatics because it induces bronchoconstriction. Sotalol also has Class III antiarrhythmic properties.

Class III (K Channel Blockers)*amiodarone*

Has properties of more than one antiarrhythmic class but is usually categorized as a class III agent. In addition to prolonging repolarization, amiodarone acts as a vasodilator and negative inotrope. **Rx:** Treatment of atrial fibrillation, atrial flutter, ventricular tachycardia. **Tox:** Pulmonary fibrosis, hepatotoxicity, microcystic deposits on the cornea, thyroid dysfunction (hypo- or hyperthyroidism).

bretylium

Prolongs the action potential by blocking K^+ channels. Also blocks norepinephrine release from postganglionic adrenergic nerve terminals. **Rx:** Refractory ventricular arrhythmias. **Tox:** Hypotension.

Class IV (Ca^{2+} Channel Blockers)*verapamil, diltiazem*

These agents bind to L-type Ca^{2+} channels and result in decreased Ca^{2+} influx; this slows the response of the SA and AV nodes. **Rx:** These drugs control ventricular rate in atrial flutter or fibrillation. **Tox:** CHF, peripheral edema, hypotension. **Other:** Nifedipine is not used as an antiarrhythmic.

DRUGS USED TO TREAT CONGESTIVE HEART FAILURE
(Chapter 22)
Cardiac Glycosides*digitalis, digitoxin*

These agents inhibit the Na^+/K^+ /ATPase pump, which ultimately results in more

intracellular Ca^{2+} and a positive inotropic effect. They also slow conduction through the AV node. **Rx:** CHF, atrial fibrillation, or atrial flutter. **Tox:** Nausea, vomiting, blurred vision, headache.

Bipyridine Derivatives

amrinone, milrinone

These agents inhibit phosphodiesterase, which subsequently results in increased cardiac contractility. **Rx:** Treatment of acute CHF. **Tox:** Nausea, vomiting, thrombocytopenia, arrhythmias.

Vasodilators

isosorbide dinitrate

Nitrates cause the release of nitric oxide, which relaxes veins and arteries; veins are dilated predominantly. **Rx:** Treatment of hypertension, CHF, and angina. **Tox:** Tachycardia, orthostatic hypotension.

hydralazine

Increases cGMP, which leads to dephosphorylation of myosin and relaxation of arteriolar smooth muscle. **Rx:** Treatment of moderate hypertension, CHF. **Tox:** Lupus-like syndrome (☞ board question), hypotension, reflex tachycardia, palpitations, angina, nausea, diarrhea.

β Agonists

dobutamine

Increases cardiac contractility by stimulating β receptors. **Rx:** Treatment of acute CHF. **Tox:** Arrhythmias.

dopamine

Stimulates β and dopamine receptors. **Rx:** CHF, shock, and hypotension. **Tox:** Arrhythmias.

ACE Inhibitors

captopril, enalapril

These agents block the conversion of angiotensin I to angiotensin II. **Rx:** Treatment of mild to moderate hypertension, CHF. **Tox:** Cough, hyperkalemia, dizziness; proteinuria and renal failure in patients with bilateral renal artery stenosis.

Diuretics

furosemide, ethacrynic acid, hydrochlorothiazide

See listing below under **DIURETICS** (Chapter 23).

DIURETICS (CHAPTER 23)

Carbonic Anhydrase Inhibitors

acetazolamide

Inhibits carbonic anhydrase in the proximal convoluted tubule. **Rx:** Treatment of glaucoma, mountain sickness, metabolic alkalosis. **Tox:** Paraesthesias, metabolic acidosis, interstitial nephritis. **Other:** Contraindicated in patients with hepatic or renal disease.

Loop Diuretics

furosemide, ethacrynic acid, bumetanide

These agents inhibit the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter in the thick ascending limb of the loop of Henle. **Rx:** Treatment of edematous states such as congestive heart failure. **Tox:** Hypokalemia, hypocalcemia, hyperuricemia.

Thiazides

hydrochlorothiazide

Inhibits the Na^+/Cl^- transporter in the early segment of the distal convoluted tubule. **Rx:** Treatment of hypertension, edema, CHF, nephrogenic diabetes insipidus. **Tox:** Hypokalemia, hyperglycemia, hyponatremia, hyperlipidemia, hyperuricemia.

K^+ -Sparing Diuretics

amiloride, triamterene

These K^+ -sparing diuretics work by inhibiting luminal Na^+ from entering the principal cells of the late distal convoluted tubule and collecting tubule. **Rx:** Hypertension, CHF. **Tox:** Hyperkalemia, hyponatremia, gynecomastia. **Other:** Very weak efficacy; usually used in conjunction with another diuretic.

spironolactone

Competitive antagonist of aldosterone at the aldosterone receptor in the distal convoluted tubule and collecting tubule.

Rx: Treatment of edema due to CHF, cirrhosis, primary aldosteronism. **Tox:** Hyperkalemia, gynecomastia, hyponatremia.

Osmotic Diuretics

mannitol

Increases oncotic pressure intravascularly and therefore pulls fluid away from tissues.

Rx: Rapid decrease of intracranial or intraocular pressure; maintenance of urine output. **Tox:** Pulmonary edema, dehydration, hypernatremia. **Other:** Given IV only because of poor absorption.

ANTIANGINAL DRUGS (Chapter 24)

Nitrates

nitroglycerin, isosorbide nitrate, amyl nitrate

Nitrates cause the release of nitric oxide, which relaxes veins and arteries (veins are dilated predominantly). **Rx:** Treatment of hypertension, CHF, angina, and cyanide poisoning. **Tox:** Tachycardia, orthostatic hypotension.

Calcium Channel Blockers

diltiazem, verapamil, nifedipine

These agents bind to L-type Ca^{2+} channels and result in decreased Ca^{2+} influx, which slows the response of the SA and AV nodes. **Rx:** Beneficial in angina because they reduce afterload and decreasing heart rate; also used to treat hypertension, arrhythmias. **Tox:** Heart block, CHF, peripheral edema, hypotension.

β Blockers

propranolol, timolol, metoprolol, atenolol

See previous listing in this Power Review under **ADRENERGIC ANTAGONISTS (Chapter 9)**.

ANTICOAGULANTS, FIBRINOLYTICS, AND OTHER ANTIPLATELET DRUGS (Chapter 25)

heparin

Enhances the activity of antithrombin III more than 1000-fold by binding to antithrombin III and inducing a structural

change that exposes the active site of antithrombin III. **Rx:** Used in pulmonary embolism, stroke, MI, unstable angina, DVT. **Tox:** Bleeding, thrombocytopenia. **Other:** Effects of heparin are reversed with protamine sulfate.

warfarin

An oral anticoagulant that interferes with vitamin K- dependent clotting factors (II, VII, IX, X). **Rx:** Treatment of venous thrombosis, pulmonary emboli, atrial fibrillation, and other conditions requiring long-term anticoagulation. **Tox:** Hemorrhage. **Other:** Contraindicated in pregnancy. Effects of warfarin are reversed with Vitamin K or fresh frozen plasma.

tissue plasminogen activator (TPA, alteplase)

A "second-generation" recombinant human thrombolytic enzyme that activates plasminogen bound to fibrin; this, in theory, limits systemic bleeding. **Rx:** Acute MI resulting from coronary thrombosis, DVT, pulmonary emboli. **Tox:** Hemorrhage.

urokinase

An enzyme generated by the human kidney which directly converts plasminogen to plasmin. **Rx:** Treatment of acute pulmonary embolism. **Tox:** Systemic bleeding.

streptokinase

Binds with plasminogen, causing a conformational change which then catalyzes the conversion of other plasminogen molecules into plasmin. **Rx:** Coronary thrombolysis, acute MI, severe pulmonary emboli. **Tox:** Bleeding, fever, hypersensitivity with continued use.

aminocaproic acid

Binds to plasmin and plasminogen; this prevents plasmin from binding to fibrin and therefore inhibits clot lysis. **Rx:** Used for control of hemorrhage due to hypofibrinogenemia; counteracts the effects of urokinase, TPA, and streptokinase. **Tox:** Myopathy, hypotension, intravascular thrombosis.

ANTHYPERLIPIDEMIC DRUGS (Chapter 26)

Bile Acid Resins*cholestyramine, colestipol*

These bile acid resins prevent absorption of dietary cholesterol and bile acids; they also increase hepatic LDL receptors. **Rx:** Used to lower LDL plasma levels. **Tox:** Indigestion, nausea, lipid-soluble vitamin deficiency.

HMG-CoA Inhibitors*lovastatin, simvastatin, pravastatin*

These HMG-CoA reductase inhibitors block endogenous cholesterol synthesis, forcing hepatocytes to increase LDL receptors. **Rx:** Hypercholesterolemia. **Tox:** Gastro-intestinal distress. **Other:** Rhabdomyolysis may occur when these agents are used with niacin or gemfibrozil.

niacin

Mechanism of action not well understood; appears to decrease adipose tissue lipolysis, which in turn reduces circulating free fatty acids. **Rx:** Hypertriglyceridemia. **Tox:** A cutaneous flush and pruritus are the most common problems. Liver toxicity—must monitor LFTs at least every 6 months. Hyperglycemia, hyperuricemia, nausea, constipation.

clofibrate, gemfibrozil

Mechanism of action not well understood. These drugs increase activity of lipoprotein lipase, a plasma enzyme that degrades chylomicrons and VLDL. **Rx:** Very effective for hypertriglyceridemia. **Tox:** Skin rash is common with gemfibrozil. Clofibrate has been associated with an increase in hepatobiliary and gastrointestinal neoplasms. **Other:** These drugs also potentiate the effects of anticoagulant drugs.

DRUGS USED TO TREAT ANEMIA (Chapter 27)

iron

Most commonly given through oral

Cyanocobalamin
(vitamin B₁₂)

ferrous iron supplementation. **Rx:** Treatment of iron-deficient microcytic anemia. **Tox:** Gastrointestinal disturbances are the most common side effects. If the dose is sufficiently high, shock, metabolic acidosis, and even death can occur.

A cofactor in the transfer of one-carbon units, which is a step necessary in the synthesis of DNA. **Rx:** Treatment of megaloblastic anemia, pernicious anemia, tabes dorsalis. **Tox:** None.

folic acid

Necessary for the transfer of one-carbon fragments in the synthesis of purine and pyrimidine bases. **Rx:** Treatment of megaloblastic anemia; critical in pregnancy to reduce risk of neural tube defects. **Tox:** No known adverse effects.

erythropoietin

A glycoprotein produced by the kidney. **Rx:** Treatment of anemias associated with end-stage renal failure and bone marrow failure. **Tox:** The only toxicity is associated with an excessive increase in red blood cell count.

DRUGS USED TO TREAT ASTHMA, COUGHS, AND COLDS (CHAPTER 28)

Sympathomimetics

**metaproterenol, terbutaline,
albuterol, salmeterol**

These β_2 agonists work by increasing cyclic AMP, which results in bronchodilation. **Rx:** Drugs of choice for acute relief of bronchospasm. **Tox:** Tremor, tachycardia.

Corticosteroids

**beclomethasone, flunisolide,
triamcinolone, fluticasone**

These glucocorticoids reduce inflammation by reversing mucosal edema, decreasing the permeability of capillaries, and inhibiting the release of leukotrienes. **Rx:** Treatment of asthma and other reactive airway diseases. **Tox:** Minimal toxicities if given through aerosol; rarely, adrenal suppression.

Anticholinergics

ipratropium

Inhibits acetylcholine receptors found in smooth muscle; minimizes bronchial secretion and bronchoconstriction. **Rx:** Treatment of asthma, COPD. **Tox:** Dry mouth, sedation.

Methylxanthines

theophylline

Phosphodiesterase inhibitor that increases cAMP and results in bronchodilation; also has some anti-inflammatory effects. **Rx:** Treatment of asthma, COPD. **Tox:** Palpitations, tachycardias, arrhythmias, headaches.

Leukotriene Inhibitors

zileuton, zafirlukast

Zileuton is a 5-lipoxygenase inhibitor; zafirlukast is an LTD₄ receptor antagonist. **Rx:** Treatment of asthma. **Tox:** With zileuton, some cases of hepatitis have been reported; with zafirlukast, drug allergy has been reported.

cromolyn sodium

An effective drug that stabilizes the membrane of mast cells and prevents histamine and leukotriene release, probably by blocking calcium gates. **Rx:** Prophylaxis against asthmatic attacks. **Tox:** Well tolerated but can cause cough or wheezing.

HYPOTHALAMIC AND PITUITARY HORMONES (Chapter 29)

oxytocin

Stimulates the force and frequency of uterine contractions; causes milk ejection by contracting myoepithelial cells surrounding mammary alveoli. **Rx:** Induction of labor in patients with delivery complications; control of postpartum and postabortal uterine hemorrhage. **Tox:** Hypertensive episodes, uterine rupture.

vasopressin

Activates receptors on the renal tubule cells to increase the number and insertion of water channels in the kidney collecting

tubule; also vasoconstricts vessels. **Rx:** Used in the treatment of central diabetes insipidus; infused to stop variceal bleeding. **Tox:** Headache, nausea, abdominal cramps, hypertension, bradycardia.

THYROID AND ANTITHYROID DRUGS (Chapter 30)

Drugs Used to Treat Hypothyroidism

levothyroxine sodium

A synthetic analog of thyroxine (T_4). **Rx:** Treatment of hypothyroidism. **Tox:** Cardiac effects (palpitations, hypertension, arrhythmias), thyrotoxicosis heat intolerance.

liothyronine sodium

A synthetic analog of triiodothyronine (T_3). **Rx:** Treatment of hypothyroidism; Adjuvant in the treatment of myxedema coma because of its rapid onset of action. **Tox:** Palpitations, hypertension, arrhythmias, thyrotoxicosis.

Drugs Used to Treat Hyperthyroidism

propylthiouracil, methimazole

These thioamides stop the iodination and coupling of the thyroglobulin molecule; therefore, monoiodotyrosine (MIT) and diiodotyrosine (DIT) cannot be produced. Without MIT and DIT, it is impossible to produce T_3 and T_4 . **Rx:** Treatment of hyperthyroidism. **Tox:** Agranulocytosis—rare but most important side effect to watch for; also rash, edema, joint pain.

perchlorate, thiocyanate

These ionic inhibitors competitively inhibit the concentration of iodide in the thyroid gland by blocking the iodide transport mechanism. **Rx:** Previously used to treat Graves' disease, their use today has diminished. **Tox:** Perchlorate has caused fatal aplastic anemia.

potassium iodide

Inhibits release of T_3 and T_4 . Iodide also decreases the vascularity and size of the thyroid gland. **Rx:** Rarely used today as sole therapy; most often used prior to surgery or in conjunction with a

thioamide and propranolol in thyrotoxic crisis. **Tox:** Anaphylactoid reaction—angioedema and swelling of the larynx. Chronic iodide intoxication (iodism)—brassy taste and burning in the mouth, soreness of the teeth and gum, swelling of the eyelids, coryza and sneezing that simulates a cold, respiratory problems, enlarged parotid and submaxillary glands.

SEX STEROIDS AND INHIBITORS (Chapter 31)

Estrogens

estradiol, ethinyl estradiol, estrone, mestranol

These agents bind to cytosolic receptors and travel to the nucleus where they regulate estrogen-sensitive gene transcription. **Rx:** Used in the treatment of dysmenorrhea, in oral contraceptives, and in hormone replacement therapy. **Tox:** Hypertension, thrombophlebitis, thromboembolism, endometrial hyperplasia.

Estrogen Antagonists

tamoxifen

Blocks estrogen receptors. **Rx:** Treatment of breast cancer. **Tox:** Hot flashes.

clomiphene

Blocks estrogen receptors. **Rx:** Treatment of female infertility. **Tox:** Multiple births, excessive enlargement of ovaries.

Progestins

medroxyprogesterone, norethindrone

These agents bind to cytosolic receptors and travel to the nucleus, where they stimulate transcription of progestin-responsive genes. **Rx:** Used in the treatment of dysfunctional uterine bleeding and endometriosis, and in contraception. **Tox:** Decreased HDL, increased blood pressure, thrombophlebitis and weight gain.

Progestin Antagonists

danazol

An agonist at progestin, glucocorticoid, and androgen receptors. **Rx:** Treatment of endometriosis. **Tox:** Edema, acne, weight gain.

mifepristone

Inhibits progesterin by blocking receptors.
Rx: Abortifacient. **Tox:** Heavy bleeding.

Androgens

methyltestosterone, fluoxymesterone, oxymetholone

These agents bind to cytosolic receptors and then migrate to the nucleus, where they stimulate transcription of testosterone-responsive genes. **Rx:** Treatment of hypogonadism and anemia; chemotherapy for estrogen-sensitive breast cancers. **Tox:** Prostatic hypertrophy, priapism, cholestatic jaundice, hepatocellular carcinoma.

CORTICOSTEROIDS AND INHIBITORS (Chapter 32)

Glucocorticoids

cortisol, prednisone, triamcinolone, dexamethasone, betamethasone

These agents bind to cytosolic receptors and then are taken to the nucleus, where they stimulate transcription of glucocorticoid responsive genes. **Rx:** Anti-inflammatory agents; used in the treatment of autoimmune disease and adrenocortical insufficiency. **Tox:** Adrenal suppression, immunosuppression, osteoporosis, salt retention, hyperglycemia, steroid psychosis. **Other:** Dexamethasone is used for treatment of cerebral edema and diagnosis of Cushing's disease. Betamethasone is used for induction of surfactant synthesis in premature newborns.

Mineralocorticoids

fludrocortisone, deoxycorticosterone

Synthetic analogs of aldosterone. **Rx:** Treatment of Addison's disease; replacement therapy after adrenalectomy. **Tox:** CHF, hypokalemia, anaphylaxis.

INSULINS AND ORAL HYPOGLYCEMIC DRUGS (Chapter 33)

Insulins

regular insulin, NPH, ultralente

Insulin binds to tyrosine kinase receptors on cell membranes; it does not enter the nucleus. **Rx:** Insulin-dependent diabetes. **Tox:** Hypoglycemia, insulin allergy, insulin antibody, lipodystrophy.

Other: The three forms of insulin differ in their onset of action and duration of action.

Sulfonylureas

chlorpropamide, tolbutamide, glyburide, glipizide, glimepiride, acetohexamide

These agents stimulate the release of endogenous insulin from β cells of the pancreas, and increase binding of insulin to target tissues and receptors. The initial step in the facilitation of endogenous insulin release is binding and blocking ATP-sensitive K^+ channels. **Rx:** Type II diabetes. **Tox:** Hypoglycemia, gastrointestinal distress, pruritus, agranulocytosis (rare).

Biguanides

metformin

Decreases hepatic glucose production and intestinal glucose absorption, and increases peripheral glucose uptake; also, improves insulin sensitivity. **Rx:** Treatment of type II diabetes. **Tox:** Lactic acidosis, diarrhea, nausea, upset stomach.

α -Glucosidase Inhibitors

acarbose (Precose)

Delays the absorption of glucose from the gastrointestinal tract. The advantage of this drug is that it does not cause a reactive hypoglycemia. **Rx:** Type II diabetes. **Tox:** Gastrointestinal distress (abdominal pain, diarrhea).

Thiazolidinediones

trogglitazone

It improves target cell response to insulin by binding to nuclear receptors that regulate the transcription of a number of insulin-responsive genes. It is dependent upon insulin for activity. **Rx:** Type II diabetes. **Tox:** Hepatotoxicity, hypoglycemia.

DRUGS AFFECTING CALCIUM HOMEOSTASIS (Chapter 34)

Drugs Used to Treat Hypocalcemia

calcium gluconate, calcium chloride

Calcium supplements. **Rx:** Treatment of hypocalcemia. **Tox:** Hypercalcemia.

ergocalciferol

Vitamin D agent that increases calcium absorption from the intestine. **Rx:** Treatment of hypocalcemia. **Tox:** Hypercalcemia.

Drugs Used to Treat Hypercalcemia

calcitonin

Decreases osteoclastic bone resorption and calcium reabsorption from the kidney; does not usually affect bone formation. **Rx:** Paget's disease of the bone, hypercalcemia. **Tox:** GI effects, flushing, redness or tingling of the face.

Bisphosphates

etidronate, pamidronate

Short-chain compounds that act upon osteoclasts to reduce both the formation and dissolution of hydroxyapatite crystals. **Rx:** Treatment of Paget's disease of the bone, malignancy-induced hypercalcemia. **Tox:** Osteomalacia, nausea, diarrhea.

Miscellaneous Agents

plicamycin

Inhibits the effect of parathyroid hormone (PTH) on osteoclasts, or blocks the effects of vitamin D. **Rx:** Paget's disease of the bone, hypercalcemia. **Tox:** Nausea, vomiting, loss of appetite, hypocalcemia.

ANTI-INFLAMMATORY DRUGS AND ACETAMINOPHEN (Chapter 35)

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

acetylsalicylic acid (aspirin)

Irreversibly inhibits cyclooxygenase, blocking production of prostaglandin and thromboxane. **Rx:** Used in the treatment of a wide variety of diseases involving inflammation, fever, or pain (arthritis, headache, dysmenorrhea); MI prophylaxis (antiplatelet effects). **Tox:** Renal failure, salicylism (tinnitus, decreased hearing, vertigo), GI bleeding, respiratory alkalosis, and metabolic acidosis.

ibuprofen, indomethacin, naproxen (many more examples)

These agents *reversibly* inhibit cyclooxygenase. **Rx:** Used to reduce fever and inflammation; as analgesics for arthritis, gout, and muscle aches and pains; and as anticoagulants secondary to antiplatelet activity. **Tox:** GI bleeding, interstitial nephritis, papillary necrosis.

Para-aminophenol Derivatives

acetaminophen

Acts by inhibiting prostaglandin synthesis in the CNS. It has little effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory effects. **Rx:** Used for fever, mild to moderate pain. Patients with peptic ulcer disease or hemophilia tolerate acetaminophen better than aspirin. **Tox:** Hepatotoxicity. **Other:** Treat overdoses with N-acetylcysteine.

DRUGS USED TO TREAT GOUT (Chapter 36)

colchicine

Inhibits microtubulin function; this, in turn, prevents migration of neutrophils to areas of inflammation. **Rx:** Both for treatment of acute attacks and for prophylaxis. **Tox:** Gastrointestinal distress (vomiting, diarrhea, abdominal pain), alopecia. With chronic use: leukopenia, agranulocytosis, aplastic anemia are possible.

indomethacin

Reversibly inhibits cyclooxygenase; consequently, the production of prostaglandins and thromboxane, which are responsible for inflammation, are reduced. **Rx:** Drug of choice for acute gout. **Tox:** Headache, vertigo, abdominal distress, renal toxicity, rash.

probenecid, sulfipyrazone

At therapeutic concentrations, these uricosuric agents increase uric acid excretion by inhibiting uric acid reabsorption in the proximal tubule. **Rx:** Treatment of chronic gout and asymptomatic hyperuricemia. These drugs are not indicated in acute attacks of gout. **Tox:** These agents can precipitate an

acute attack of gouty arthritis in the early stages of treatment. Other side effects are gastrointestinal distress and occasional hypersensitivity reactions.

allopurinol

Inhibits the enzyme xanthine oxidase. **Rx:** Gout, recurrent renal stones, tumor lysis syndrome. **Tox:** Usually well tolerated but can cause hypersensitivity reactions (allergic dermatitis, fever), gastrointestinal distress (diarrhea, abdominal pain). Peripheral vasculitis and neuritis are rare complications.

AUTOCIDS AND AUTOCID ANTAGONISTS (Chapter 37)

Serotonin Agonists

bupirone, sumatriptan

These agents stimulate serotonin (5-HT) receptors. **Rx:** Bupirone—anxiolytic; sumatriptan—treatment of migraine headaches. **Tox:** Bupirone—drowsiness; sumatriptan—dizziness and tingling.

Serotonin Antagonists

ondansetron, cyproheptadine

These agents competitively bind and inhibit serotonin (5-HT) receptors. **Rx:** Ondansetron is used in the treatment of nausea and vomiting associated with surgery. Cyproheptadine is used in the treatment of carcinoid tumor and post-gastrectomy dumping syndrome, as well as allergic conditions. **Tox:** Ondansetron—hepatotoxicity, constipation. Cyproheptadine—anticholinergic effects.

Ergot Alkaloids

bromocriptine, ergonovine, ergotamine

These agents act on 5-HT, dopamine, and α -adrenoreceptors; they diminish cerebral vascular pulsations. **Rx:** Treatment of hyperprolactinemia (bromocriptine), migraine (ergotamine), postpartum hemorrhage (ergonovine and

ergotamine), motion sickness, nausea and vomiting, insomnia. **Tox:** Gastrointestinal disturbances; ergotism (St. Anthony's fire), which consists of vasospasm possibly resulting in gangrene; CNS psychosis; abortion if patient is pregnant.

DRUGS USED TO TREAT GI DISORDERS (CHAPTER 38)

Antacids

calcium carbonate

Neutralizes gastric acid. **Rx:** Treatment of peptic ulcer and reflux disease. **Tox:** Constipation, diarrhea.

Proton Pump Inhibitors

omeprazole, lansoprazole

Parietal cell proton pump inhibitors. **Rx:** Treatment of Zollinger-Ellison syndrome, peptic ulcer disease. **Tox:** Diarrhea, abdominal pain, headache.

Mucosal Protectors

sucralfate

Binds to necrotic peptic ulcer tissue and acts as a barrier to acid and other destructive substances. **Rx:** Peptic ulcer disease. **Tox:** GI discomfort, constipation.

misoprostol

A prostaglandin E₁ analog thought to stimulate gastric secretion of mucous. **Rx:** Peptic ulcer disease. **Tox:** Diarrhea; can cause unwanted uterine contractions leading to abortion.

Histamine Blockers

cimetidine, ranitidine, famotidine, nizatidine

These agents competitively block histamine at H₂ receptors. **Rx:** Treatment of peptic ulcer disease, Zollinger-Ellison syndrome. **Tox:** Mental status changes, antiandrogen effects; inhibits P₄₅₀ system. **Other:** Famotidine and nizatidine have similar effects but do not cause mental status changes in the elderly.

Prokinetic Agents***metoclopramide***

Antagonist at D_2 receptors in gastric smooth muscle. **Rx:** Treatment of gastropareses, gastroesophageal reflux. **Tox:** Extrapyramidal side effects, diarrhea, agranulocytosis.

ANTINEOPLASTIC DRUGS (Chapter 39)

Antibiotics***dactinomycin***

Binds to the double helix of DNA and forms a dactinomycin-DNA complex that inhibits DNA-dependent RNA polymerase. **Rx:** Treatment of Wilms' tumor, rhabdomyosarcoma. **Tox:** Bone marrow depression, nausea, vomiting, dermatological effects, sensitization to radiation.

doxorubicin, daunorubicin

These agents intercalate with the sugar-phosphate backbone of DNA, causing DNA breaks. This results in inhibition of DNA and RNA synthesis. **Rx:** Doxorubicin—ALL and AML, breast and lung cancer. Daunorubicin—AML and ALL. **Tox:** Irreversible cardiotoxicity (board question), myelosuppression, nausea, vomiting, alopecia.

bleomycin

Combines with iron and forms a complex that reacts with oxygen to produce free radicals. This causes strand scission and DNA fragmentation. **Rx:** Testicular carcinoma, squamous carcinomas, Hodgkin's disease. **Tox:** Pulmonary fibrosis (board question), fever and chills, mucocutaneous toxicity, hypersensitivity.

mitomycin

Reduces to a bi- or trifunctional alkylating agent that inhibits DNA synthesis. **Rx:** Cervical carcinoma, bladder carcinoma. **Tox:** Nausea, vomiting, loss of appetite, bone marrow suppression, hemolytic-uremic syndrome (rare).

Antimetabolites***6-mercaptopurine***

A purine antimetabolite that inhibits DNA and RNA synthesis. **Rx:** ALL,

methotrexate

AML. Tox: Bone marrow suppression, hepatotoxicity, GI mucositis.

Folic acid analog that inhibits dihydrofolate reductase. **Rx:** Treatment of ALL; carcinomas of the breast, lung, ovary, bladder, and neck; chorio-carcinoma; psoriasis; and rheumatoid arthritis. **Tox:** Myelosuppression, GI hemorrhagic enteritis, neurotoxicity.

5-fluorouracil

Converted to 5F-dUMP, which inhibits RNA synthesis. **Rx:** Breast carcinoma, colon carcinoma. **Tox:** Leukopenia, diarrhea, infection, esophagitis, stomatitis.

Alkylating Agents

mechlorethamine

Forms an ethylenimmonium that cross-links strands of RNA and DNA. **Rx:** Used for Hodgkin's disease. **Tox:** Myelosuppression, nausea, vomiting, amenorrhea, phlebitis at site of injection.

cyclophosphamide

The metabolite of this drug, called phosphoramidate mustard, cross-links DNA and RNA strands. **Rx:** Ovarian and breast carcinoma, Hodgkin's and non-Hodgkin's lymphoma, all of the leukemias. **Tox:** Nausea, hemorrhagic cystitis, skin pigmentation, hair loss, gonadal and bone marrow suppression.

lomustine

Inhibits DNA, RNA, and protein synthesis by causing DNA strand disruption. **Rx:** Melanoma, GI cancers, brain tumors. **Tox:** Nausea, vomiting, bone marrow suppression.

streptozocin

Alkylating agent that inhibits DNA synthesis by cross-linking strands of DNA. **Rx:** Pancreatic carcinomas. **Tox:** Renal failure, nausea, vomiting.

cisplatin

Cross-links DNA and causes strand disruption. **Rx:** Testicular and bladder carcinomas. **Tox:** Nephrotoxicity, ototoxicity, bone marrow suppression.

carboplatin

Same mechanism of action as cisplatin.

Rx: Ovarian carcinomas. **Tox:** Bone marrow suppression, anemia.

busulfan

Cross-links strands of DNA. **Rx:** Drug of choice for chronic myelocytic leukemia (CML). **Tox:** Bone marrow suppression.

carmustine

Inhibits DNA, RNA, and protein synthesis. **Rx:** Brain tumors, Hodgkin's and non-Hodgkin's lymphomas, GI cancers, multiple myeloma. **Tox:** Bone marrow suppression, pulmonary fibrosis.

dacarbazine

Inhibits DNA and RNA synthesis via formation of carbonium ions. **Rx:** Hodgkin's lymphoma. **Tox:** Nausea, vomiting, bone marrow suppression, hepatotoxicity.

Plant Alkaloids

vinblastine

Binds to tubulin and inhibits the polymerization of microtubules. **Rx:** Testicular tumors, lymphomas. **Tox:** Myelosuppression.

vincristine

Binds to tubulin and inhibits the polymerization of microtubules. **Rx:** Lymphomas, Wilms' tumor, leukemias. **Tox:** Peripheral neuropathy, alopecia.

etoposide

Binds to DNA topoisomerase II and induces breaks in the DNA strands. **Rx:** Testicular and lung carcinomas, Hodgkin's and non-Hodgkin's lymphomas, Kaposi's sarcoma. **Tox:** Bone marrow suppression, gastrointestinal distress.

Hormones

glucocorticoids

These agents bind to nuclear receptors that code for glucocorticoid responsive genes. **Rx:** Hodgkin's lymphoma, acute leukemia. **Tox:** Hyperglycemia, increased number of infections, osteoporosis, cataracts, hypertension.

tamoxifen

A competitive antagonist at estrogen receptors. **Rx:** Estrogen receptor-positive

leuprolide

breast cancer. **Tox:** Hot flashes, nausea, vomiting.

Gonadotropin-releasing hormone (GnRH) analog that inhibits the release of follicle-stimulating hormone (FSH) and leutenizing hormone (LH). **Rx:** Endometriosis, prostatic carcinoma. **Tox:** Hot flashes, impotence

PENICILLINS (Chapter 41)

Natural Penicillins

penicillin G, penicillin V

These agents inhibit cell wall synthesis by blocking peptidoglycan translocation. **Rx:** Treatment of gram-positive cocci, gram positive bacilli spirochelos, neisseria and most anaerobic infections (except *B. fragilis*). **Tox:** Hypersensitivity reactions (anaphylaxis, urticaria, nephritis), Coombs'-positive hemolytic anemia. GI distress, cation toxicity

Aminopenicillins

ampicillin

Like natural penicillins, it inhibits cell wall synthesis by interfering with the cross-linking of peptidoglycans. **Rx:** Drug of choice for enterococcus and *Listeria*; also used to treat infections by gram-positive and some gram-negative organisms such as *E. coli*, *Salmonella*, *Shigella*. **Tox:** Drug-induced hemolytic anemia, allergic reactions (rashes, anaphylaxis, fever, urticaria, joint swelling).

amoxicillin

An oral equivalent of ampicillin.

Antipseudomonal Penicillins

mezlocillin, ticarcillin, azlocillin, carbenicillin, piperacillin

Mechanism of action similar to natural penicillin. **Rx:** Treatment of gram-negative bacilli infections, especially *Pseudomonas*, *Proteus*, and *Serratia*. **Tox:** Same as for natural penicillins.

Antistaphylococcal Penicillins

methicillin, nafcillin, oxacillin, dicloxacillin,

Mechanism of action similar to that of natural penicillins; however, these drugs

cloxacillin

are resistant to penicillinase. **Rx:** Treatment of methicillin-sensitive staphylococci. **Tox:** Methicillin in particular induces interstitial nephritis. Most of these drugs can induce a granulocytopenia and Coombs'-positive hemolytic anemia.

CEPHALOSPORINS AND OTHER CELL WALL SYNTHESIS INHIBITORS (Chapter 42)

First-Generation Cephalosporins

cephapirin, cefadroxil, cephradine, cephalexin, cefazolin, cephalothin

These agents inhibit cell wall synthesis by blocking cross-linking of peptidoglycans. **Rx:** Excellent gram-positive coverage. **Tox:** Hypersensitivity reactions, potential nephrotoxicity.

Second-Generation Cephalosporins

cefamandole, cefotetan, cefonicid, cefprozil, cefaclor, cefuroxime, loracarsef, cefoxitin

Mechanism of action similar to that of first-generation cephalosporins. **Rx:** Increased gram-negative coverage and decreased gram-positive coverage as compared with first-generation cephalosporins; also some anaerobic coverage. **Tox:** Hypersensitivity reactions, alcohol intolerance; bleeding with cefamandole and cefotetan.

Third-Generation Cephalosporins

cefixime, cefoperazone, ceftazidime, ceftriaxone, moxalactam, ceftizoxime, cefotaxime

Mechanism of action similar to that of first-generation cephalosporins. **Rx:** Greatest gram-negative coverage of the cephalosporin group; least gram-positive coverage. **Tox:** Ceftriaxone causes biliary stasis, Coombs'-positive hemolytic anemia, hypersensitivity reactions.

Other Cell Wall Inhibitors

vancomycin

Binds to cell wall precursors and prevents polymerization of peptidoglycans. **Rx:** Used against methicillin-resistant *Staphylococcus aureus* (MRSA), for serious gram-positive infections, in penicillin-allergic patients, and for pseudomembranous colitis caused by

Clostridium difficile. **Tox:** Ototoxicity, nephrotoxicity; flushing of face when infused rapidly (known as “red man syndrome”).

imipenem/cilastatin

Imipenem inhibits cell wall synthesis while cilastatin inhibits metabolism of the drug in the proximal convoluted tubule by renal dehydropeptidase. **Rx:** Effective against aerobic and anaerobic gram-positive and gram-negative organisms. **Tox:** Seizures in patients with renal dysfunction; cross-allergy with penicillin. **Other:** Imipenem is an extremely broad-spectrum antibiotic but does *not* cover MRSA.

aztreonam

Inhibits peptidoglycan synthesis. **Rx:** Used against gram-negative aerobic rods; *not* effective against gram-positive or anaerobic bacteria. **Tox:** GI distress, elevated liver enzymes, skin rashes. **Other:** Minimal cross-reactivity with penicillins.

PROTEIN SYNTHESIS INHIBITORS (Chapter 43)

chloramphenicol

Binds reversibly to the 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase step. **Rx:** Treatment of typhoid fever caused by *Salmonella*; topical treatment of eye infections; effective against both gram-positive and gram-negative organisms. **Tox:** Aplastic anemia. Bone marrow depression causes a dose-related nausea and vomiting. The drug is toxic for newborn infants; ingestion by the mother during late pregnancy may result in gray baby syndrome with vomiting, flaccidity, hypothermia, and possibly death.

Macrolides

erythromycin, clarithromycin, azithromycin

These agents bind to the 50S ribosome and prevent the translocation step of protein synthesis. **Rx:** Chlamydial infections and diphtheria due to

Corynebacterium diphtheriae. Drug of choice for community-acquired *Mycoplasma* and *Legionella* pneumonias. Also used against streptococcal and pneumococcal infection in penicillin-allergic patients. **Tox:** Epigastric distress, cholestatic jaundice, hypersensitivity reactions (fever, rashes, eosinophilia). **Other:** Azithromycin and clarithromycin are second-generation macrolides with increased activity against *Haemophilus influenzae* and *Mycobacterium avium* complex.

Lincosamides

clindamycin

A bacteriostatic agent that binds to the 50S ribosomal subunit and inhibits protein synthesis by interfering with translocation (similar to erythromycin). **Rx:** Anaerobic infections that cause diseases such as empyema, lung abscess, and aspiration pneumonia; gram-positive cocci. **Tox:** Pseudomembranous colitis, granulocytopenia, erythema multiforme, skin rashes, inhibition of neuromuscular transmission.

Aminoglycosides

gentamicin, streptomycin, tobramycin, amikacin, netilmicin, spectinomycin

Bind to the 30S ribosome and inhibit protein synthesis by blocking the formation of an initiation complex or causing the misreading mRNA. **Rx:** Life-threatening gram-negative microbial infections; especially effective against *Pseudomonas aeruginosa*, *Enterobacter* species, *Klebsiella* species. **Tox:** Ototoxicity, nephrotoxicity. **Other:** Spectinomycin is effective only for gonorrhea. Amikacin is uniquely resistant to inactivating enzymes.

neomycin, kanamycin

These agents work the same way as the other aminoglycosides. **Rx:** Given orally for treatment of bacteria in the intestinal lumen. Treatment of hepatic encephalopathy. **Tox:** Ototoxicity, nephrotoxicity; intestinal malabsorption, neuromuscular blockade, respiratory paralysis.

Tetracyclines

*doxycycline, minocycline,
demeclocycline*

These agents bind reversibly to the 30S subunit of the bacterial ribosome, blocking the binding site of amino acyl-tRNA to its acceptor site on the mRNA.

Rx: Tetracyclines are broad-spectrum antibiotics. They are bacteriostatic for gram-positive and gram-negative organisms, including *Borrelia* (cause of Lyme disease), chlamydiae, mycoplasmas, *Treponema* species, *Vibrio cholera*, *Francisella tularensis* (cause of tularemia), and *Rickettsia* species. Also used for acne. **Tox:** Gastrointestinal distress; tooth discoloration in children younger than 7 years; liver toxicity; photosensitivity; vestibular reactions (dizziness, nausea, and vomiting can occur with minocycline).

Other: Contraindicated in pregnant women and nursing mothers. Ca^{2+} -containing substances impair absorption.

QUINOLONES AND UTI DRUGS (Chapter 44)

*ofloxacin, ciprofloxacin,
norfloxacin*

Bactericidal agents that inhibit bacterial DNA topoisomerase II (DNA gyrase).

Rx: Active against many gram-negative organisms but not anaerobes; used to treat UTIs, respiratory infections caused by *Hemophilus influenzae*, *Legionella*, and *Pseudomonas*, GI infections, prostatitis, and gonorrhea. **Tox:** May cause cartilage damage in children; can cause nausea, headache, dizziness, crystalluria, and photosensitivity. **Other:** Can increase levels of theophylline.

nitrofurantoin

Nitrofurantoin alters various bacterial enzymes and DNA

Rx: Treatment of UTIs, especially those caused by *E. coli* and enterococci. **Tox:** Nausea, vomiting, acute pneumonitis, neuropathies, hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

FOLATE ANTAGONISTS (Chapter 45)

sulfamethoxazole, sulfisoxazole, silver sulfadiazine, sulfasalazine, sulfacetamide

The sulfonamides, because they resemble PABA, bind and competitively inhibit dihydropteroate synthetase, the enzyme responsible for combining PABA and pteridine. **Rx:** Simple urinary tract infections due to *E. coli* and *Klebsiella* species; ulcerative colitis (sulfasalazine is best because it is poorly absorbed); burn infections (mafenide, silver sulfadiazine); ocular infections, especially *Chlamydia trachomatis* (sulfacetamide); nocardiosis; *Pneumocystis carinii* pneumonia. **Tox:** Rashes, angioedema, Stevens-Johnson syndrome, gastrointestinal distress (nausea and vomiting), hemolytic anemia in patient with G6PD deficiency, crystalluria/hematuria, kernicterus in infants, phototoxicity. **Other:** Contraindicated in pregnant women and newborns because of the risk of kernicterus.

trimethoprim

Stops the conversion of dihydrofolate to tetrahydrofolate by inhibiting the enzyme dihydrofolate reductase. Trimethoprim is very often combined with sulfamethoxazole; this compound is known as co-trimoxazole. **Rx:** Effective in treating complicated or recurrent UTIs. Treatment of bacterial prostatitis, gonorrhea, acute chronic bronchitis, acute otitis media, toxoplasmosis. Drug of choice for *Pneumocystis carinii* pneumonia. Sometimes given in a nebulized or vaporized form. **Tox:** Dermatological effects, gastrointestinal effects (nausea, vomiting), hematological effects (leukopenia, megaloblastic anemia), renal impairment in patients with renal disease, headache, depression. AIDS patients are especially susceptible to developing rashes.

ANTIFUNGAL DRUGS (Chapter 46)

amphotericin B

Amphotericin B binds to ergosterol and forms pores or channels within the

**ketoconazole, fluconazole,
miconazole, itraconazole**

cell membrane. This allows electrolytes to leak from the cell, resulting in cell death.

Rx: Treatment of aspergillosis and infection by *Candida*, *Blastomyces dermatitidis*, *Histoplasma*, *Cryptococcus*, and *Coccidioides*. **Tox:** Renal impairment (80% of patients exhibit decreased GFR and changes in renal tubular function), hypotension, fever, chills, anemia. Because of its high toxicity, amphotericin is nicknamed “amphoterrible.”

These agents block conversion of lanosterol into ergosterol by blocking a P_{450} enzyme. **Rx:** *Ketoconazole*—Most commonly used to treat histoplasmosis; effective against most of the same fungi as amphotericin B; can also be used against griseofulvin-resistant dermatophytes. *Fluconazole*—Very effective for oral candidiasis, cryptococcosis, and coccidioidomycosis. *Itraconazole*—Drug of choice for blastomycosis; has similar spectrum of action as ketoconazole. **Tox:** *Ketoconazole*—GI irritation, endocrine abnormalities due to inhibition of steroid synthesis (gynecomastia, impotence, decreased libido, menstrual irregularities), hepatic dysfunction. *Fluconazole*—Has no endocrinological effects, but can cause GI irritation and rashes. *Itraconazole*—Can cause GI irritation, hypokalemia, headache. **Other:** Miconazole and clotrimazole are very similar to ketoconazole in their mechanism of action and clinical uses. However, these agents are usually only given topically and therefore do not have systemic side effects. Fluconazole penetrates the CNS; the others do not.

flucytosine

Enters fungal cells through a cytosine-specific permease and is first converted to 5-fluorouracil (5-FU). Subsequently it is converted to 5-fluorodeoxyuridylic acid (5F-dUMP). This acid inhibits thymidylate synthetase, an essential enzyme in the production of DNA. **Rx:** Given in

combination with amphotericin B for treatment of systemic *Candida* and *Cryptococcus* infections. **Tox:** Hematological effects (reversible neutropenia, thrombocytopenia, bone marrow depression), hepatic dysfunction, gastrointestinal disturbances (nausea, vomiting).

griseofulvin

Enters susceptible fungal cells and inhibits microtubule function; may also inhibit synthesis and polymerization of nucleic acids. Accumulates in the newly synthesized keratin-containing tissues and is fungistatic. **Rx:** Effective only against dermatophytes, including *Trichophyton*, *Microsporum*, and *Epidermophyton*. **Tox:** GI irritation, headache, hepatotoxicity. **Other:** Contraindicated in acute intermittent porphyria; induces P₄₅₀ system activity; may be teratogenic.

nystatin

Binds to ergosterol in fungal cell membranes and creates pores. **Rx:** Used topically for local *Candida* infections. **Tox:** Very mild side effects (local irritation).

ANTIPROTOZOAL DRUGS (Chapter 47)

primaquine

A tissue schizonticide and gametocide that forms cellular oxidants that are toxic to the protozoa. **Rx:** Eradicates the liver stages of *P. vivax* and *P. ovale* (primary as well as secondary exoerythrocytic forms); not effective against the erythrocytic stage of malaria. Gametocidal for all four *Plasmodium* species and can therefore be used to interrupt transmission of the disease. **Tox:** Methemoglobinemia, GI distress, headaches, pruritus, hemolytic anemia in G6PD-deficient patients. Granulocytopenia and agranulocytosis can occur in patient who have lupus or arthritis.

chloroquine

Multiple mechanisms of action: (1) increases the pH of plasmodial food vacuoles, which results in an inability of

the parasite to digest hemoglobin; (2) inhibits the plasmodial enzyme heme polymerase, which is responsible for eliminating toxic hemoglobin breakdown by-products; (3) disrupts plasmodial DNA. **Rx:** Acts against erythrocyte forms of *Plasmodium falciparum*, *P. vivax*, and *P. ovale*. Since it is a blood schizonticide, it will not eradicate hypnozoites and is therefore not useful for the treatment of relapsing malaria caused by *P. ovale* or *P. vivax*. Also has anti-inflammatory effects and is sometimes used in autoimmune disorders. **Tox:** Peripheral neuropathies, myocardial depression with ECG changes, retinal damage (requires routine ophthalmologic exams), auditory impairment, toxic psychosis.

quinine

A blood schizonticide that complexes with dsDNA and prevents strand separation. **Rx:** Useful against malarial strains resistant to other agents such as chloroquine. **Tox:** GI distress. Cinchonism (tinnitus, headache, dizziness). Hemolytic anemia. **Other:** Elevates digoxin levels.

mefloquine

Structural analog of quinine. **Rx:** Treatment of malaria secondary to *Plasmodium*. **Tox:** Gastrointestinal distress, headache, dizziness, hallucinations.

pyrimethamine

Selectively inhibits plasmodial dihydrofolate reductase, thereby depriving the organism of tetrahydrofolate, a cofactor in the biosynthesis of purines and pyrimidines. **Rx:** Effective alone against *P. falciparum*; used in the treatment of toxoplasmosis when combined with sulfadiazine. **Tox:** Folic acid deficiency in high doses, rash, GI distress, hemolysis, renal damage.

sodium stibogluconate

Unclear mechanism of action. **Rx:** Treatment of leishmaniasis. **Tox:** GI distress, cardiac arrhythmias.

suramin

Unclear mechanism of action. **Rx:** Treatment of African sleeping sickness

before CNS involvement (use melarsoprol if CNS is involved). **Tox:** GI effects (nausea, vomiting).

metronidazole

Forms a cytotoxic metabolite that interacts with protozoal DNA and RNA.

Rx: Treatment of pseudomembranous colitis, *Giardia* and *Trichomonas vaginalis* infection, and amebiasis. Also used in triple therapy with bismuth and amoxicillin against *H. pylori*. **Tox:** Gastrointestinal distress, CNS effects, paraesthesias, discoloration of urine.

Other: Will cause a disulfiram-like reaction when used with ethanol.

pentamidine

Binds DNA and may inhibit replication, but exact mechanism is unknown. **Rx:** Treatment of *Pneumocystis carinii* pneumonia. **Tox:** Nephrotoxicity, pancreatitis, hypotension.

ANTHELMINTIC DRUGS (Chapter 48)

mebendazole, thiabendazole

These agents interfere with the synthesis of microtubules and decreases glucose uptake. **Rx:** Drugs of choice for pinworm (*Enterobius vermicularis*), whipworm (*Trichuris trichiura*). Also used against *Necator americanus* and *Ascaris lumbricoides*. **Tox:** Nausea and vomiting.

pyrantel pamoate

Acts as a depolarizing neuromuscular blocking agent, causing persistent activation of nicotinic acetylcholine receptors and thus paralysis of the worm. **Rx:** Drug of choice in *Ascaris* infections; can also be used for pinworm and hookworm. **Tox:** Nausea, vomiting, headaches, rash.

diethylcarbamazine

Precise mechanism of action is unknown. **Rx:** Treatment of filariasis. **Tox:** Usually mild but may include headache, nausea and vomiting, lymphadenopathy, hypotension, and tachycardia.

ivermectin

Increases GABA transmission, which results in paralysis of parasites. **Rx:** Treatment of river blindness caused by *Onchocerca volvulus*. **Tox:** Intense itching, skin rashes.

praziquantel

Causes tetanic muscle contraction by increasing the permeability of cell membranes to Ca^{2+} . **Rx:** schistosomiasis, trematode infections and citicericosis. **Tox:** GI distress, dizziness, drowsiness. **Other:** Contra-indicated in pregnant women and nursing mothers.

niclosamide

Inhibits mitochondrial anaerobic phosphorylation of ADP within cestodes. **Rx:** Drug of choice for most cestode (tapeworm) infections. **Tox:** Rashes and fever.

ANTIVIRAL DRUGS (Chapter 49)

acyclovir

Monophosphorylated by a herpes enzyme called thymidine kinase. Later it is di- and triphosphorylated by the host cell. The active triphosphate form is then incorporated into viral DNA, causing premature DNA-chain termination. **Rx:** Treatment of herpes simplex, varicella-zoster virus, and Epstein-Barr virus. **Tox:** Renal dysfunction, neurotoxicity (delirium, tremor, seizures), diarrhea, headache, local irritation.

trifluridine

A thymidine analog. **Rx:** Used topically for eye infections, HSV types 1 and 2. **Tox:** minimal due to topical application.

amantadine, rimantadine

These agents inhibit viral uncoating. **Rx:** Prophylaxis of influenza A in elderly and immunosuppressed. **Tox:** Insomnia, dizziness, ataxia; these symptoms are less common with rimantadine because it does not cross the blood-brain barrier.

foscarnet

Inhibits viral replication by blocking viral DNA polymerase, which prevents chain elongation. **Rx:** Treatment

of CMV retinitis in immunocompromised patients. **Tox:** Nephrotoxicity; electrolyte abnormalities such as hypocalcemia and hypomagnesemia; seizures; and fever.

ganciclovir

It is triphosphorylated into its active form and then inhibits viral DNA polymerase. Incorporation into DNA also terminates chain elongation. **Rx:** Drug of choice for cytomegalovirus. **Tox:** Bone marrow suppression, seizures, renal dysfunction.

zidovudine (AZT)

After being triphosphorylated into its active form, it inhibits viral reverse transcriptase and causes chain termination. **Rx:** HIV. **Tox:** Bone marrow suppression, (thrombocytopenia, granulocytopenia), headaches, occasionally seizures. **Other:** Side effects are potentiated if zidovudine is given with drugs that decrease glucuronidation, such as acetaminophen, probenecid, or indomethacin.

didanosine (ddI)

Inhibits viral transcriptase and, after incorporation into DNA, acts as a chain terminator. **Rx:** Treatment of HIV. **Tox:** Peripheral neuropathy, pancreatitis.

ribavirin

Mechanism of action not fully elucidated, but is thought to be related to decreasing the intracellular stores of guanosine triphosphate and inhibiting 5-cap formation of viral mRNA. **Rx:** Treatment of infants and young children who are suffering from RSV bronchiolitis and pneumonia. Also used occasionally for treating influenza A, and lassa fever B.

Tox: Dose-

dependent hemolytic anemia, elevated bilirubin.

DRUGS USED TO TREAT TUBERCULOSIS AND LEPROSY (Chapter 50)

isoniazid

Inhibits the synthesis of mycolic acids, which are unique to the mycobacterial cell walls. **Rx:** Treatment of active tuberculosis; tuberculosis prophylaxis in

rifampin

those who are close contacts of TB patients or who have a positive PPD. **Tox:** Potentially fatal hepatitis, peripheral neuropathy, rashes, skin eruptions. **Other:** Half-life depends on whether patient is a slow or fast acetylator.

Inhibits the β -subunit of DNA-dependent RNA polymerase; suppresses RNA synthesis by blocking chain initiation. **Rx:** Treatment of tuberculosis; used in combination with dapsone to treat leprosy; used in combination with erythromycin to treat Legionnaire's disease. Also used prophylactically for close contacts of patients diagnosed with *Haemophilus influenzae* meningitis. **Tox:** Causes urine, sweat, tears, and other secretions to become red-orange in color; rash, fever, nausea and vomiting, hepatic dysfunction. **Other:** Rifampin significantly induces the P_{450} system.

ethambutol

Mechanism of action not known for certain, but it is thought to inhibit incorporation of mycolic acid into the mycobacterial cell wall. **Rx:** Treatment of tuberculosis in combination with isoniazid (INH), pyrazinamide, and rifampin. **Tox:** Optic neuritis, decreased visual acuity, and loss of red-green discrimination; may precipitate a gout attack.

pyrazinamide

Not known. **Rx:** Treatment of tuberculosis in combination with isonicotinic acid hydrazide (INH), pyrazinamide, and rifampin. **Tox:** Hepatotoxicity; gout due to the inhibition of uric acid secretion arthralgia, and myalgia.

dapsone

Inhibits folate synthesis by acting as a competitive antagonist of para-aminobenzoic acid. **Rx:** Leprosy; *Pneumocystis carinii* pneumonia in HIV patients. **Tox:** Hemolysis in patients with G6PD deficiency, lupus erythematosus, methemoglobinemia.

Appendices

Appendices

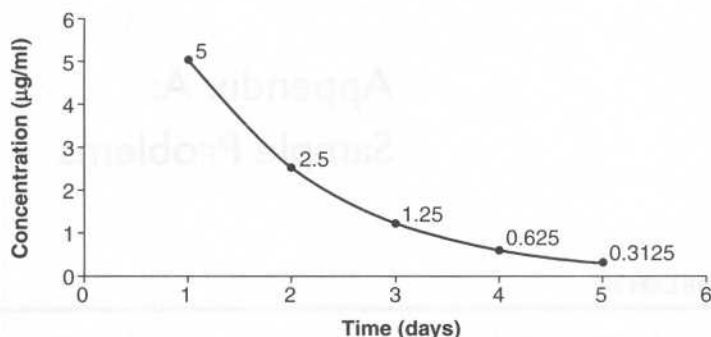


Figure A. Plasma concentration vs. time for Drug Y (see Problem #1).

(maintenance dose) to keep the average plasma concentration of Drug X at 5 µg/ml.

3. If Drug X's toxic dose is 20 µg/ml, what is its therapeutic index?

ANSWERS AND EXPLANATIONS

Problem #1

- $t_{1/2} = 1$ day.** From inspection of the graph, you can see that it takes exactly 1 day for the concentration of Drug Y to be reduced by one half.
- $V_D = 3$ L.** To determine the volume of distribution, you must extrapolate the data to "Time 0" to find C_0 , the initial plasma concentration of Drug Y. The plasma concentration on Day 1 was 5 µg/ml. Since the half-life is 1 day, the initial concentration of Drug Y (C_0) = 10 µg/ml. Since the route of administration was intravenous, 100% of the drug will reach the systemic circulation ($F_0 = 1$). Use the initial concentration to determine the volume of distribution:

$$V_D = \text{drug dose (D)} \div \text{plasma concentration (C}_0\text{)} = 30 \text{ mg} \div 10 \text{ µg/ml} = 3 \text{ L}$$

3. **Cl = 1.44 ml/min.** Use the information in Answers 1 and 2 to find the clearance:

$$Cl = (0.693 \times V_D) \div t_{1/2} = (0.693 \times 3000 \text{ ml}) \div 1440 \text{ minutes} = 1.44 \text{ ml/min}$$

4. **$C_{av} = 2$ mg/ml. It would take at least 4 days to reach this value.** Again, since this is an intravenous delivery, 100% of the drug will reach the systemic circulation ($F_0 = 1$). If the infusion rate (dose over time, or D/T) is set to 2.88 mg/min, and the clearance was determined to be 1.44 ml/min, the average plasma concentration at steady state would be

Appendix A: Sample Problems

PROBLEM #1

The graph in **Figure A** plots the results of an experiment in which a 30-mg IV bolus of Drug Y was given at Time 0, and measurements of plasma concentration of Drug Y were taken over the next 5 days. The labeled data points indicate the actual **plasma concentration in $\mu\text{g/ml}$** for each of the 5 days.

Using the information contained in the graph, answer the questions below concerning the pharmacokinetic parameters of Drug Y. Assume that Drug Y is distributed instantly throughout its volume of distribution. *Remember:* $1 \mu\text{g/ml} = 1 \text{ mg/L}$; $1 \text{ day} = 1440 \text{ minutes}$.

1. Determine the half-life ($t_{1/2}$).
2. Determine the volume of distribution (V_D).
3. Determine the clearance (Cl).
4. An infusion pump is set to deliver a constant 2.88 mg/min of Drug Y into an identical experimental subject. Assuming no initial bolus was given, predict the average plasma concentration (C_{av}) at steady state for Drug Y. How long would it take for the plasma concentration to reach this state?

PROBLEM #2

A 55-year-old man weighing 100 kg presents to the ER after experiencing severe chest pain. Drug X is an anticoagulant that has recently been approved for use in the management of acute myocardial infarction. The following pharmacokinetic data are available for Drug X:

Oral availability = 50%

Clearance = $10 \text{ ml/min} \cdot \text{kg}$

Volume of distribution (V_d) = 1.0 L/kg

Therapeutic concentration (conc) = $5 \mu\text{g/ml}$

1. As an attending in the ER, your goal is to administer an intravenous bolus (loading dose) of Drug X so that the therapeutic concentration is reached rapidly. What is the loading dose of Drug X?
2. After some time, the patient's condition is stabilized, but further management using Drug X is necessary. Calculate the infusion rate

maintained at **2 mg/ml**. This can be explained using the following equation:

$$C_{av} = D/T \div Cl = 2.88 \text{ mg/min} \div 1.44 \text{ mg/min} = \mathbf{2 \text{ mg}}$$

It takes approximately **4 half-lives** to reach the steady state plasma concentration on a continuous maintenance infusion. Since the $T_{1/2}$ was determined to be 1 day, it would take **4 days** to reach the average plasma concentration of 2 mg.

Problem #2

- 1. Loading dose = 500 mg.** The bolus depends on the V_d :

$$\text{Loading dose} = \text{conc} \times V_d = 5 \text{ } \mu\text{g/ml} \times 1000 \text{ ml/kg} = 500 \text{ mg}$$

- 2. The infusion rate (maintenance dose) is 5 mg/min.** The maintenance dose (D/T) depends on the clearance (Cl):

$$D/T = \text{conc} \times Cl = 5 \text{ } \mu\text{g/ml} \times 10 \text{ ml/min*kg} \times 100 \text{ kg} = 5 \text{ mg/min}$$

- 3. The therapeutic index is 4.** The therapeutic index equals the ratio of toxic dose to therapeutic dose:

$$\text{Therapeutic index} = 20 \text{ } \mu\text{g/ml} \div 5 \text{ } \mu\text{g/ml} = \mathbf{4}$$

*Remember to match units while performing all of the above calculations

Appendix B: Recommended Antimicrobial Agents Against Selected Organisms

<i>Bacterial Species</i>	<i>Recommended Antimicrobial Agent*</i>
<i>Alcaligenes xylosoxidans</i> (<i>Achromobacter xylosoxidans</i>)	IMP, AP Pen, ceftaz, MER
<i>Acinetobacter calcoaceticus</i> — <i>baumannii</i> complex	IMP or MER or [FQ + (amikacin or ceftaz)]
<i>Actinomyces israeli</i>	AMP or Pen G
<i>Aeromonas hydrophila</i>	FQ
<i>Arcanobacterium</i> (C.) <i>haemolyticum</i>	Erythromycin
<i>Bacillus anthracis</i> (anthrax)	CIP or doxycycline
<i>Bacillus cereus</i> , <i>B. subtilis</i>	Vancomycin, clindamycin
<i>Bacteroides fragilis</i> (ssp. <i>fragilis</i>), "DOT" group of <i>bacteroides</i>	Metronidazole
<i>Bartonella</i> (<i>Rochalimaea</i>) <i>henselae</i> , <i>quintana</i>	Erythromycin
<i>Bordetella pertussis</i>	Erythromycin

<i>Bacterial Species</i>	<i>Recommended Antimicrobial Agent*</i>
<i>Borrelia burgdorferi</i> , <i>B. afzelii</i> , <i>B. garinii</i>	Ceftriaxone, cefuroxime axetil, doxycycline, amoxicillin
<i>Borrelia recurrentis</i>	Doxycycline
<i>Brucella</i> sp.	Doxycycline + either gentamicin or streptomycin
<i>Burkholderia (Pseudomonas)</i> <i>cepacia</i>	TMP/SMX or IMP or CIP
<i>Burkholderia (Pseudomonas)</i> <i>pseudomallei</i>	Ceftaz (continuous IV) (AAC 39: 2356, 1995) or AM/CL
<i>Campylobacter jejuni</i>	Erythromycin
<i>Campylobacter fetus</i>	IMP
<i>Capnocytophaga ochracea</i> (DF-1)	Clindamycin
<i>Campylobacter canimorsus</i> (DF-2)	AM/CL
<i>Chlamydia pneumoniae</i>	Doxycycline
<i>Chlamydia trachomatis</i>	Doxycycline or azithromycin
<i>Chryseobacterium (Flavo-</i> <i>bacterium) meningosepticum</i>	Vancomycin
<i>Citrobacter diversus (koseri)</i> , <i>C. freundii</i>	IMP or MER
<i>Clostridium difficile</i>	Metronidazole (po) <i>continued</i>

continued

TMP/SMX: trimethoprim/sulfamethoxazole; AP Pen: antipseudomonal penicillin; P Ceph: parenteral cephalosporins; PRSP: penicillinase-resistant synthetic penicillins; APAG: antipseudomonal aminoglycosides; FQ: fluoroquinolones [ciprofloxacin, ofloxacin, lomefloxacin, enoxacin, pefloxacin, levofloxacin, trovafloxacin (not norfloxacin or sparfloxacin unless specifically indicated)]; AMP: ampicillin; CIP: ciprofloxacin; IMP: imipenem + cilastatin; RIF: rifampin; AM/CL: amoxicillin clavulanate; TC/CL: ticarcillin clavulanate; AM/SB: ampicillin sulbactam; Ceftaz: ceftazidime; PIP/TZ: piperacillin-tazobactam; MER: meropenem; DOT group: *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*; NUS: not available in the U.S.; BL/BLI: β -lactam/ β -lactamase inhibitor (AM/CL, TC/CL, AM/SB, or PIP/TZ)

Bacterial Species	Recommended Antimicrobial Agent*
<i>Clostridium perfringens</i>	Pen G \pm clindamycin
<i>Clostridium tetani</i>	Metronidazole or pen G
<i>Corynebacterium jeikeium</i>	Vancomycin
<i>C. diphtheriae</i>	Erythromycin
<i>Coxiella burnetii</i> (Q fever)	
Acute disease	Doxycycline
Chronic disease	CIP or doxycycline + RIF
<i>Ehrlichia chaffeensis</i> , <i>Ehrlichia phagocytophila</i>	Doxycycline
<i>Eikenella corrodens</i>	Penicillin G or AMP or AM/CL
<i>Enterobacter</i> spp. (<i>aerogenes</i> , <i>cloacae</i>)	IMP or MER or (AP Pen + APAG)
<i>Enterococcus faecalis</i>	Penicillin G (AMP). Add gentamicin for endocarditis or meningitis.
<i>Enterococcus faecium</i> , β -lactamase +, high-level aminoglycoside resist., vancomycin resist.	No regimen of proven efficacy. Consultation recommended if pt has endocarditis or other life-threatening infection.
<i>Erysipelothrix rhusiopathiae</i>	Penicillin G or AMP
<i>Escherichia coli</i>	Sensitive to BL/BLI, cephalosporins, FQ, TMP/SMX, APAG, nitrofurantoin, IMP. Selection of drug depends on site of infection, i.e., UTI multiple po agents; meningitis P Ceph 3 or MER.
<i>Francisella tularensis</i> (tularemia)	Streptomycin or gentamicin
<i>Gardnerella vaginalis</i> (bacterial vaginosis)	Metronidazole
<i>Hafnia alvei</i>	Same <i>Enterobacter</i> spp.
<i>Helicobacter pylori</i>	Bismuth (B) + metronidazole (M) + tetracycline (T) + omeprazole (O) = 96% cure. BMT \times 1 wk or BCT \times 1 wk = 86%–90% cure.

Bacterial Species	Recommended Antimicrobial Agent*
<i>Hemophilus aphrophilus</i>	Penicillin or AMP \pm gentamicin, or AM/SB \pm gentamicin
<i>Hemophilus ducreyi</i> (chancroid)	Azithromycin or ceftriaxone
<i>Hemophilus influenzae</i> Meningitis, epiglottitis & other life-threatening illness	Cefotaxime, ceftriaxone
Non-life threatening illness	AM/CL, O Ceph 2/3, TMP/SMX, AM/SB
<i>Klebsiella pneumoniae, oxytoca</i>	P Ceph 3, FQ
<i>Klebsiella ozaenae</i> (rhino- scleromatis)	FQ
<i>Lactobacillus</i> sp.	Pen G or AMP \pm gentamicin
<i>Legionella</i> sp. (36 species recognized)	Erythromycin \pm RIF; FQ; or azithromycin
<i>Leptospira interrogans</i>	Penicillin G or doxycycline
<i>Leuconostoc</i>	Pen G or AMP
<i>Listeria monocytogenes</i>	AMP
<i>Moraxella</i> (<i>Branhamella</i>) <i>catarrhalis</i>	AM/CL or O Ceph 2/3, TMP/SMX
<i>Morganella</i> sp.	IMP or MER or P Ceph 3 or 4 or FQ
<i>Mycoplasma pneumoniae</i>	Erythromycin, azithromycin, clari- thromycin, dirithromycin, or FQ
<i>Neisseria gonorrhoeae</i> (gonococcus)	Ceftriaxone, cefixime, cefpodoxime

continued

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Bacterial Species	Recommended Antimicrobial Agent*
<i>Neisseria meningitidis</i> (meningococcus)	Penicillin G
<i>Nocardia asteroides</i>	TMP/SMX, sulfonamides (high dose)
<i>Nocardia brasiliensis</i>	TMP/SMX, sulfonamides (high dose)
<i>Pasteurella multocida</i>	Penicillin G
<i>Plesiomonas shigelloides</i>	CIP
<i>Proteus mirabilis</i> (indole -)	AMP
<i>Proteus vulgaris</i> (indole +)	P Ceph 3 or FQ
<i>Providencia</i> sp.	Amikacin or P Ceph 3 or FQ
<i>Pseudomonas aeruginosa</i>	AP Pan, P Ceph 3 AP, IMP, tobramycin
<i>Rhodococcus</i> (<i>C. equi</i>)	Vancomycin
<i>Rickettsiae</i> species	Doxycycline
<i>Salmonella typhi</i>	FQ, ceftriaxone
<i>Serratia marcescens</i>	P Ceph 3, IMP, MER, FQ
<i>Shigella</i> sp.	FQ
<i>Staph. aureus</i> , methicillin-susceptible	PRSP
<i>Staph. aureus</i> , methicillin-resistant	Vancomycin
<i>Staph. epidermidis</i>	Vancomycin
<i>Stenotrophomonas</i> (<i>Xanthomonas</i> , <i>Pseudomonas</i>) <i>maltophilia</i>	TMP/SMX
<i>Streptobacillus moniliformis</i>	Penicillin G or doxycycline
<i>Streptococcus, anaerobic</i> (peptostreptococcus)	Penicillin G

<i>Bacterial Species</i>	<i>Recommended Antimicrobial Agent*</i>
<i>Streptococcus pneumoniae</i>	
Penicillin-susceptible	Penicillin G
Penicillin-resistant (MIC ≥ 2.0)	Vancomycin
<i>Streptococcus pyogenes</i> (Groups A, B, C, G, F), <i>Strep. milleri</i> (<i>constellatus</i> , <i>intermedius</i> , <i>anginosus</i>)	Penicillin G or V (some add gentamicin for serious Group B strep infections)
<i>Vibrio cholerae</i>	Doxycycline, FQ
<i>Vibrio parahaemolyticus</i>	Antibiotic rx does not ↓ course
<i>Vibrio vulnificus</i> , <i>alginolyticus</i> , <i>damsela</i>	Doxycycline \pm ceftaz
<i>Yersinia enterocolitica</i>	TMP/SMX or FQ
<i>Yersinia pestis</i> (plague)	Streptomycin, gentamicin

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Appendix C:

Comparison of Antimicrobial Spectra*

*These comparisons are generalizations; there are major differences between countries, areas and hospitals depending upon antibiotic usage patterns—verify for individual location.

PENICILLINS, IMPENEM, AZTREONAM, METRONIDAZOLE, FLUOROQUINOLONES

Organisms			Pen ⁿ ase Res. Penicillins		Amino- Penicillins		Anti-Pseudomonal Penicillins						Fluoroquinolones													
	Penicillin G	Penicillin V	Methicillin	Nafcillin/Oxacillin	Cloxacillin	Dicloxacillin	Amp/Amox	Amox/Clav	Amp/Subl	Ticarcillin	Ticar/Clav	Pip/Tazo	Mezlocillin	Piperacillin	Imipenem	Meropenem	Aztreonam	Metronidazole	Ciprofloxacin	Ofloxacin	Lomefloxacin	Pefloxacin	Levofloxacin	Sparfloxacin	Trovafloxacin	Grepafloxacin
GRAM-POSITIVE:																										
<i>Strep.</i> Group A,B,C,G	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	±	±	0	0	+	+	+	+
<i>Strep. pneumoniae</i>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	±	±	0	0	+	+	+	+
<i>Viridans strep.</i> , <i>milleri</i>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0			+	+	+	+
+ <i>Enterococcus faecalis</i>	+	+	0	0	0	0	+	+	+	±	±	±	±	±	±	±	0	0	±	±		0	+	+	+	+
<i>Enterococcus faecium</i>	±	±	0	0	0	0	+	+	+	±	±	±	±	±	±	±	0	0	0	0		0	0	±	±	±
<i>Staph. aureus</i> (MSSA)	0	0	+	+	+	+	0	+	+	0	+	+	0	0	+	+	0	0	+	+	+	+	+	+	+	+
<i>Staph. aureus</i> (MRSA)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	±	±	±	±
<i>Staph. epidermidis</i>	0	0	±	±	±	±	±	+	+	±	±	+	0	0	0	+	0	0	+	+	+	+	+	+	+	+
<i>C. jeikeium</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				0	0	
<i>L. monocytogenes</i>	+	0	0	0	0	0	+	+	+	+	+	+	+	+	+	+	0	0	+					±		+
GRAM-NEGATIVE:																										
<i>N. gonorrhoeae</i>	0	0	0	0	0	0	0	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+
<i>N. meningitidis</i>	+	0	0	0	0	0	+	+	+	+	+	+	+	+	+	+	+	0	+	+		+	+	+	+	+
<i>M. catarrhalis</i>	0	0	0	0	0	0	0	+	+		+		+		+	+	+	0	+	+	+	+	+	+	+	+
<i>H. influenzae</i>	0	0	0	0	0	0	±	+	+	0	+	+	0	±	+	+	+	0	+	+	+	+	+	+	+	+
<i>E. coli</i>	0	0	0	0	0	0	±	+	+	±	+	+	±	±	+	+	+	0	+	+	+	+	+	+	+	+
<i>Klebsiella</i> sp.	0	0	0	0	0	0	0	+	+	±	+	+	±	±	+	+	+	0	+	+	+	+	+	+	+	+
<i>Enterobacter</i> sp.	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+
<i>Serratia</i> sp.	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	+	+	0	+	+	+		+	+	+	+
<i>Salmonella</i> sp.	0	0	0	0	0	0	±	+	+	+	+	+	+	0	+	+	+	0	+	+		+	+	+	+	+
<i>Shigella</i> sp.	0	0	0	0	0	0	±	+	+	+		+	+	+	+	+	+	0	+	+		+	+	+	+	+

<i>Proteus mirabilis</i>	0	0	0	0	0	0	+	+	+	+	+	+	+	+	+	+	+	+	+
<i>Proteus vulgaris</i>	0	0	0	0	0	0	0	+	+	+	+	+	+	+	+	+	+	+	+
<i>Providencia</i> sp.	0	0	0	0	0	0	0	+	+	+	+	+	+	+	+	+	+	+	+
<i>Morganella</i> sp.	0	0	0	0	0	0	0	±	+	+	+	+	+	+	+	+	+	+	+
<i>Citrobacter</i> sp.	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	+	+	+	+
<i>Aeromonas</i> sp.	0	0	0	0	0	0	0	+	+	+	+	+	+	+	+	+	+	+	+
<i>Acinetobacter</i> sp.	0	0	0	0	0	0	0	0	+	+	+	+	+	+	+	0	0	+	+
<i>Ps. aeruginosa</i>	0	0	0	0	0	0	0	0	0	+	+	0	0	+	+	+	0	+	+
<i>B. (Ps.) cepacia</i> [§]	0	0	0	0	0	0	0	0	0	+	+	+	+	+	0	0	0	0	0
<i>S. (X.) maltophilia</i> [§]	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	±	+
<i>Y. enterocolitica</i>	0	0	0	0	0	0	0	±	±	±	+	+	+	+	0	+	0	+	+
<i>Legionella</i> sp.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
<i>P. multocida</i>	+	+	0	0	0	0	+	+	+	+	+	+	+	+	0	+	+	+	+
<i>H. ducreyi</i>	+						0	+	+	0	0	0	0	0					
MISC.:																			
<i>Chlamydia</i> sp.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
<i>M. pneumoniae</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
ANAEROBES:																			
<i>Actinomyces</i>	+	±	0	0	0	0	+	+	+					+	+	0	0	0	±
<i>Bacteroides fragilis</i>	0	±	0	0	0	0	0	+	+	±	+	+	+	+	+	0	+	0	0
<i>P. melaninogenica</i> [§]	+	0	0	0	0	0	+	+	+	+	+	+	+	+	+	0	+	+	0
<i>Clostridium difficile</i>	+ ¹									+ ¹				+ ¹	+ ¹	0	+	0	+
<i>Clostridium</i> (not <i>difficile</i>)	+	+					+	+	+	+	+	+	+	+	+	0	+	±	±
<i>Peptostreptococcus</i> sp.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	±	±

+ = usually effective clinically or >60% susceptible; ± = clinical trials lacking or 30%–60% susceptible; 0 = not effective clinically or <30% susceptible.

[§]*B. melaninogenica* → *Prevotella melaninogenica*, *Pseudomonas cepacia* → *Burkholderia cepacia*, *Xanthomonas* → *Stenotrophomonas*

^oMost strains ±, can be used in UTI, not in systemic infection

Ticar/Clav = ticarcillin clavulanate; *Amp/Sulb* = ampicillin sulbactam; *Amox/Clav* = amoxicillin clavulanate; *MSSA* = methicillin-sensitive *Staph. aureus*; *MRSA* = methicillin-resistant *Staph. aureus*; *Pip/Tazo* = piperacillin tazobactam

¹No clinical evidence that penicillins or fluoroquinolones are effective for *C. difficile* enterocolitis, but they may cover this organism in mixed intra-abdominal and pelvic infections.

CEPHALOSPORINS

1st Generation	2nd Generation	3rd Generation	Oral Agents										
			Cefpodoxime-Prox.	+	+	+	+	+	+	+	+	+	+
			Cefetamet-Piv.	+	+	+	+	0	0	0	+	+	+
			Ceftibuten	+	+	0	0	0	0	0	0	0	0
			Cefixime	+	+	+	0	0	0	0	0	0	0
			Loracarbef*	+	+	+	0	+	0	+	0	0	0
			Cefurox. axetil	+	+	+	0	+	0	+	0	0	0
			Cefprozil	+	+	0	0	+	0	+	0	0	0
			Cefaclor	+	+	+	0	+	0	+	0	0	0
			Cephalexin	+	+	+	0	+	0	+	0	0	0
			Cefadroxil	+	+	+	0	+	0	+	0	0	0
			Cefepime	+	+	+	0	+	0	+	0	0	0
			Ceftazidime	+	+	+	0	+	0	+	0	0	0
			Cefoperazone	+	+	+	+	+	0	+	0	0	0
			Ceftriaxone	+	+	+	0	+	0	+	0	0	0
			Ceftizoxime	+	+	+	0	+	0	+	0	0	0
			Cefotaxime	+	+	+	0	+	0	+	0	0	0
			Cefuroxime	+	+	+	0	+	0	+	0	0	0
			Cefoxitin	+	+	+	0	+	0	+	0	0	0
			Cefotetan	+	+	+	0	+	0	+	0	0	0
			Cefonicid	+	+	+	0	+	0	+	0	0	0
			Cefmetazole	+	+	+	0	+	0	+	0	0	0
			Cefamandole	+	+	+	0	+	0	+	0	0	0
			Cephalothin	+	+	+	0	+	0	+	0	0	0
			Cefazolin	+	+	+	0	+	0	+	0	0	0

Organisms

GRAM-POSITIVE:

Strep Group A,B,C,G
 Strep. pneumoniae¹
 Viridans strep
 Enterococcus faecalis
 Staph. aureus (MSSA)
 Staph. aureus (MRSA)
 Staph. epidermidis
 C. jejuni
 L. monocytogenes

GRAM-NEGATIVE:

N. gonorrhoeae
 N. meningitidis
 M. catarrhalis
 H. influenzae
 E. coli
 Klebsiella sp.
 Enterobacter sp.
 Serratia sp.
 Salmonella sp.
 Shigella sp.
 Proteus mirabilis

<i>Proteus vulgaris</i>	0 0	± + + + + 0	+ + + + + +	0 0 0 0 0	+ + + ±
<i>Providencia</i> sp.	0 0	+ + + + + +	+ + + + + +	0 0 0 0 +	+ + +
<i>Morganella</i> sp.	0 0	+ + + + + ±	+ + + + + +	0 0 0 0 ±	0 0 0 0
<i>C. freundii</i>			0 0 +		0
<i>C. diversus</i>			+ + +		+
<i>Citrobacter</i> sp.	0	± ± + ± ± ±	+ + + + + +	0 ± 0 ±	+ + ± +
<i>Aeromonas</i> sp.	0 0	± + + + ± +	+ + + + + +		+ + +
<i>Acinetobacter</i> sp.	0 0	0 0 0 0 0 0	+ + + 0 + ±	0 0 0 0 0	0 0
<i>Ps. aeruginosa</i>	0 0	0 0 0 0 0 0	± ± ± + + +	0 0 0 0 0	0 0
<i>B. (Ps.) cepacia</i> [§]	0 0	0 0 0 0 0 0	+ + + + + ±	0 0 0 0 0	0 +
<i>S. (X.) maltophilia</i> [§]	0 0	0 0 0 0 0 0	0 0 0 ± ± 0	0 0 0 0 0	0 0
<i>Y. enterocolitica</i>	0 0	± ± +	+ + + ± ± +		+ + +
<i>Legionella</i> sp.	0 0	0 0 0 0 0 0	0 0 0 0 0	0 0 0 0 0 0	0
<i>P. multocida</i>		+	+ + +	0	+
<i>H. ducreyi</i>	+	+	+ + + +		+
ANAEROBES:					
<i>Actinomyces</i>			+ +		
<i>Bacteroides fragilis</i>	0 0	0 + ² 0 + ² + 0	0 ± 0 0 0 0	0 0 0 0	0 0 0
<i>P. melaninogenica</i> [§]		+ + + + +	+ + ± + + 0	+ + +	+
<i>Clostridium difficile</i>		+ 0	0 0 0 0		
<i>Clostridium</i> (not <i>difficile</i>)		+ + + + + +	+ + + + +	+ +	0
<i>Peptostreptococcus</i> sp.		+ + + + + +	+ + + + + +	+ + + +	+

+ = usually effective clinically or > 60% susceptible; ± = clinical trials lacking or 30%–60% susceptible; 0 = not effective clinically or < 30% susceptible; blank = data not available.

[§]*B. melaninogenicus* → *Prevotella melaninogenica*, *P. cepacia* → *Burkholderia cepacia*, *Xanthomonas* → *Stenotrophomonas*

*A 1-carbacephem best classified as a cephalosporin

¹Ceftaz 8–16x less active than cefotax/ceftriax, effective only vs *Pen-sens.* strains (AAC 39:2193, 1995). Oral cefuroxime, cefprozil, cefpodoxime most active in vitro vs resistant *S. pneumo* (PIDJ 14:1037, 1995)

²Cefotetan and cefmetazole are less active against *B. ovatus*, *B. distasonis*, *B. thetaiotamicron* MSSA = methicillin-sensitive *Staph. aureus*; MRSA = methicillin-resistant *Staph. aureus*

PENICILLINS, IMPENEM, AZTREONAM, METRONIDAZOLE, FLUOROQUINOLONES

	AMINO-GLYCOSIDES				MACROLIDES				GLYCO-PEPTIDES				URINARY TRACT AGENTS										
	Gentamicin	Tobramycin	Amikacin	Netilmicin	Chloramphenicol	Clindamycin	Erythromycin	Dithromycin	Azithromycin	Clarithromycin	Doxycycline	Minoeycline	Vancomycin	Teicoplanin	Fusidic Acid	Trimethoprim	TMP/SMX	Nitrofurantoin	Norfloxacin	Enoxacin	Rifampin	Metronidazole	Quinupristin/dalfopristin
GRAM-POSITIVE																							
<i>Strep</i> Group A,B,C,G,	0	0	0	0	+	+	+	+	+	+	+	+	+	+	+	+	±	+	0	0	+	0	+
<i>Strep. pneumoniae</i>	0	0	0	0	+	+	+	+	+	+	+	+	+	+	+	+	±	+	0	±	+	0	+
<i>Enterococcus faecalis</i>	S	S	S	S	±	0	0	0	0		0	0	+	+	+	+	0	0	0	0	0	0	0
<i>Enterococcus faecium</i>	S	0	0	0	±	0	0	0	±	0	±	0	±	±		0	0	0	0	0	+	0	+
<i>Staph. aureus</i> (MSSA)	+	+	+	+	±	+	±	±	+	+	+	+	+	+	+	±	+	+	±	+	+	0	+
<i>Staph. aureus</i> (MRSA)	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	0	0	0	0	0	0	0	+
<i>Staph. epidermidis</i>	±	±	±	±	0	0	±	±	±	±		0	+	±	+	+	±	±	±	+	+	0	+
<i>C. jeikeium</i>		0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	+
GRAM-NEGATIVE:																							
<i>N. gonorrhoeae</i>	0	0	0	0	+	0	±	±	±	±	±	±	0		+	0	±	+	+	+	+	0	+
<i>M. catarrhalis</i> [§]	+	+	+	+	+	0	+	+	+	+	+	+					+		+		+	0	+
<i>H. influenzae</i>	+	+	+	+	+	0	±	±	+	+	+	+				±	±		+	+	+	0	±
<i>Aeromonas</i>	0				+		0	+			+		0				+					0	0
<i>E. coli</i>	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	0	0
<i>Klebsiella</i> sp.	+	+	+	+	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<i>Enterobacter</i> sp.	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	±		±	+	+		0	0
<i>Serratia marcescens</i>	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	±	0	+	+		0	0
<i>Proteus vulgaris</i>	+	+	+	+	±	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+		0	0

Organisms

GRAM-POSITIVE
Strep Group A,B,C,G,
Strep. pneumoniae
Enterococcus faecalis
Enterococcus faecium
Staph. aureus (MSSA)
Staph. aureus (MRSA)
Staph. epidermidis
C. jeikeium
 GRAM-NEGATIVE:
N. gonorrhoeae
M. catarrhalis[§]
H. influenzae
Aeromonas
E. coli
Klebsiella sp.
Enterobacter sp.
Serratia marcescens
Proteus vulgaris

<i>Acinetobacter</i> sp.	0	+	0		0	0	0	0	0	±	0	0	0	0	0	±	0	0
<i>Ps. aeruginosa</i>	+	+	+	+	0	0	0	0	0	0	0	0	0	0	+	+	0	0
<i>B. (Ps.) cepacia</i> [§]	0	0	0	0	+	0	0	0	0	0	0	0	+	+	0	0	0	0
<i>S. (K) maltophilia</i> [§]	0	0	0	0	+	0	0	0	0	0	0	0	0	+	0	0	0	
<i>Y. enterocolitica</i>	+	+	+		+	0	0	0	0	+		0	+					
<i>F. tularensis</i>	+				+					+	+		+				+	0
<i>Brucella</i> sp.	+				+	0		0	0	+	+	0	0	+	+		+	0
<i>Legionella</i> sp.							+	+	+					±	+	+		+
<i>H. ducreyi</i>					+	+	+		+	0	0	0		±	+		0	
<i>V. vulnificus</i>	0	0	0		+					+		0						
MISC:																		
<i>Chlamydia trachomatis</i>	0	0	0	0	+	±	+	+	+	+	+		0	0	0	0	+	0
<i>M. pneumoniae</i>	0	0	0	0	+	0	+	+	+	+	+		0				0	+
<i>Rickettsia</i> sp.	0	0	0	0	+		±			+	+	0	0	0			0	
<i>Mobacterium avium</i>		+						+	+								0	0
ANAEROBES:																		
<i>Actinomyces</i>	0	0	0	0	+	+	+		+	+	+	+					0	
<i>Bacteroides fragilis</i>	0	0	0	0	+	+	0	0	0	0	±	±	0	+	0	0	0	+
<i>P. melaninogenica</i> [§]	0	0	0	0	+	+		+	+	+	+	0	+		0	0	+	+
<i>Clostridium difficile</i>	0	0	0	0	±						+	+			0		+	±
<i>Clostridium</i> (not <i>difficile</i>) ^{°°}					+		±	±	+	+	+	+	+	+		+	+	+

+ = usually effective clinically or > 60% susceptible; ± = clinical trials lacking or 30%–60% susceptible; 0 = not effective clinically or < 30% susceptible; S = synergistic with penicillins (ampicillin); blank = data not available. Antimicrobials such as azithromycin have high tissue penetration, and some such as clarithromycin are metabolized to more active compounds; hence, *in vivo* activity may exceed *in vitro* activity.

¹*In vitro* results discrepant, + in one study. 0 in another [JAC 31(Suppl. C):39, 1993]

²Although active *in vitro*, TMP/SMX is not clinically effective for Group A strep pharyngitis or for infections due to *E. faecalis*.

[§]*B. melaninogenica* → *Prevotella melaninogenica*, *P. cepacia* → *Burkholderia cepacia*, *Xanthomonas* → *Stenotrophomonas*

**Vancomycin, metronidazole, given po active vs *C. difficile*; IV vancomycin not effective

TMP/SMX = trimethoprim/sulfamethoxazole; MSSA = methicillin-sensitive *Staph. aureus*; MRSA = methicillin-resistant *Staph. aureus*; S = potential synergy in combination with penicillin, ampicillin, vancomycin, or teicoplanin

(Adapted with permission from Gilbert DN, Moellering RC Jr, Sande MA: *The Sanford Guide to Antimicrobial Therapy* 1998, 28th ed. Hyde Park, VT, Antimicrobial Therapy Inc., 1998.)

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